Article

Ni−Unsymmetrical Salen Complex-Catalyzed One-Pot Multicomponent Reactions for Efficient Synthesis of Biologically Active 2-Amino-3-cyano-4H-pyrans

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ABSTRACT: In this report, four new Ni(II)−unsymmetrical salen complexes, $[NiL^{1-4}]$, were prepared by refluxing $Ni(Ac)_2 \cdot 4H_2O$ with unsymmetrical salen ligands, H_2L^{1-4}. All of the synthesized ligands and complexes were characterized by various physicochemical methods. Also, the solid-state structures of $[NiL^1]$, $[NiL^2]$, and $[NiL^4]$ were defined through single-crystal X-ray diffraction methods. The catalytic potential of $[NiL^{1-4}]$ was investigated by economic and environmentally friendly one-pot-three-component reactions (using reagent: 1,3-dicarbonyls, malononitrile, benzaldehyde, or its derivatives) for the synthesis of biologically active 2-amino-3-cyano-4H-pyran derivatives (total 16 derivatives). After optimization of the reaction conditions, this new synthetic protocol by taking Ni(II)−unsymmetrical salen complexes as catalysts shows excellent conversion with a maximum yield of up to 98% of the effective catalytic products within 1 h of reaction time. In addition, it was observed that the aromatic aldehyde containing an electron-withdrawing group as a ring substituent shows better conversion (up to 98%), and the electron-donating group substituent shows similar or less conversion compared to benzaldehyde under the optimized reaction conditions. From the comparison of results between all these Ni complexes, it was found that the efficiency of the catalytic performance follows the order $[NiL^1] > [NiL^3] > [NiL^2] > [NiL^4]$. A possible reaction pathway was predicted and established through UV−vis spectroscopy. Intermediate II proposed in the reaction pathway was also trapped and characterized through ^1H and ^{13}C NMR.
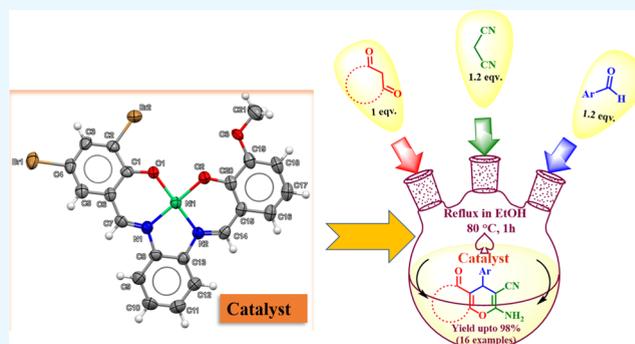
INTRODUCTION

It is well known that heterocyclic compounds have a wide range of pharmacological uses and play a significant role in biological systems.[1] Most of the currently available drug molecules and potent agrochemicals contain heterocyclic scaffolds in their overall structures. Because of their diverse applications and functions as the core of many bioactive scaffolds, heteroatom-containing organic compounds have become a key research area in chemistry. In this regard, oxygen-containing heterocyclic core structures have been attracting researchers' attention because of their wide range of applications in pharmacology. Because of their ability to degrade naturally, 2-amino-3-cyano-4H-pyrans are one of the most potent bioactive molecules found in cosmetics, dyes, and pigments, as well as agrochemicals.[2−4] There have been reports of natural products with structural similarities to 4H-pyran derivatives[5] having a variety of pharmacological properties[6] including antifungal,[7] antibacterial,[8] anticancer,[9] antitumor,[10] and calcium channel antagonists[11] (Figure 1).

Since the compound containing 4H-pyrans has outstanding biological properties and pharmaceutical applications, several synthetic methods have now been published in the literature[12−23] using several catalysts, such as carbon-based solid acids,[24] montmorillonite perchloric acid (MPA),[25] MgO NPs,[26] $Zn(L\text{-proline})_2$,[27] cyclodextrin,[28] THEIC-SBA-15,[29] urea,[30] TMDPS,[31] $Fe_3O_4@D\text{-NH-}(CH_2)_4\text{-SO}_3H$,[32] TiO_2−CNT nanocomposite,[33] $[BMIm]BF_4$,[34] Na_2CO_3,[35] Mo cata-
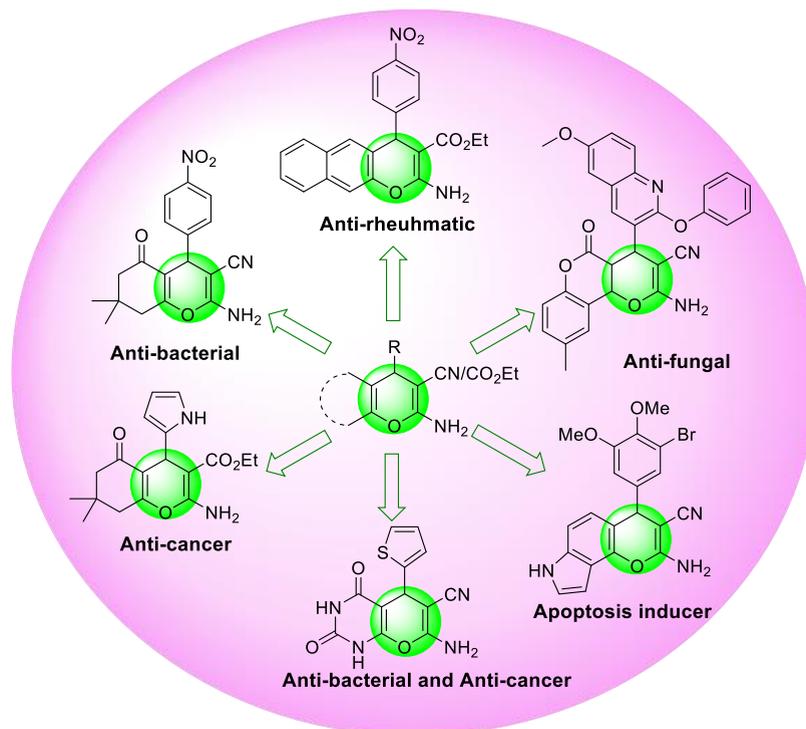
Figure 1. Structures of some biologically important 4*H*-pyran-containing compounds.

lyst,[36] nano-TiO$_2$/H$_{14}$[NaP$_5$W$_{30}$O$_{110}$],[37] V-complex,[38] [HMIM]C(CN)$_3$,[39] trifluoroethylene (TFE),[40] supported-KF,[41] urea,[42] nanozeolite,[43] Fe$_3$O$_4$@SiO$_2$-imid−PMA,[44] etc. Undoubtedly, these reported methods have their advantages. Some of those reactions have disadvantages as well, including longer reaction times, harsh reaction conditions, the corrosive nature of the reagents and solvents, limited substrate scopes, and laborious preparation procedures. Research today focuses on rapid, efficient, and multipurpose methods for the synthesis of heterocyclic compounds, and one of the essential protocols used for this purpose is transition metal catalysis.[45−47] Metal-catalyzed reactions involved multiple functional groups, occurred in mild conditions, and advanced with high stereoselectivity. The application of metal permits highly concurrent multicomponent coupling reactions that form numerous bonds and/or stereocenters in a single-pot protocol.[48−50]

However, because multicomponent reactions make it possible to synthesize a vast library of variously functionalized products from straightforward starting materials, they are particularly appealing in the field of organic chemistry.[51−55] One-pot multicomponent reactions (MCRs) are one of the most atom-economic and environmentally friendly processes with the benefit of high yield, short reaction time, and less hazardous byproduct formation. Thus, MCRs have attracted researchers' attention to synthesize biologically active organic molecules and pharmaceutical products from simple organic substrates.[51−53] These reactions can also fulfill the challenging task of synthesizing pharmaceutical and therapeutically relevant chemicals and can also help explore the synthetic strategy of these biologically active molecules.[45,51−57] The pioneer multicomponent reaction is called the Strecker reaction,[58] which includes three components: aldehydes, hydrogen cyanide, and ammonia, and the product of the reaction is α-amino acids. After this reaction, many other

reactions were testified by following multicomponent approaches such as the Biginelli reaction,[59] Gröbcke−Black-burn−Bienaymé reaction,[60] Hantzsch dihydropyridine synthesis,[61] etc. Subsequently, complexes of transition metals like Pd,[62] Cu,[63,64] Au,[65] Ag,[66] Zn,[67] and Fe[68] also showed their applicability as catalysts in MCRs. Significantly, it is also noticed that the selectivity of MCRs can be improved by the addition of a Lewis acid catalyst,[69] which is also in accordance with the principles of green chemistry.[70]

Moreover, the late transition metal nickel is present abundantly in the earth's crust, and in recent years, as the cheapest metal, the use of Ni as a catalyst is well documented. For decades, the chemistry of nickel metallo−salen complexes has attracted huge attention and broad applicability as catalysts due to their inexpensiveness and availability.[71−74] As a Lewis acid catalyst, Ni−salen units are effective in facilitating electrophilic attacks on substrates.[71,72,75] Considerable attention has also been paid to nickel Schiff base complexes as catalysts in olefin oxidation reactions.[76] Furthermore, symmetrical salen ligands have attracted researchers' attention because of their ease of synthesizing, stability, chelating properties, and attractive structural characteristics.[75,77] How-ever, in comparison to the well-known chemistry of sym-metrical salen ligands and their complexes as catalysts,[75,77] the catalytic systems containing unsymmetrical salen ligands are rarely studied due to their typical synthetic procedure. Nevertheless, unsymmetrical salen ligands provided more advantages over their symmetrical counterparts; they offered exceptionally active homo- and heterogeneous catalysts that could achieve selectivity in a variety of organic trans-formations.[78] Generally, unsymmetrical salen ligands can adjust the steric and electronic environments because the diamine in them typically contains two distinct aldehydes. The synthesis of these types of ligands and their metal complexes with modified electronic configurations in the ligand scaffold

Scheme 1. Synthetic Routes of Unsymmetrical Salen Ligands H$_2$L$^{1-4}$ (1−4)

R= C$_6$H$_4$, X = OMe, Y = Br (H$_2$L^1) (1)
R= C$_6$H$_4$, X = OMe, Y = H   (H$_2$L^2) (2)
R= C$_6$H$_4$, X = OEt, Y = H   (H$_2$L^3) (3)
R= C$_2$H$_4$, X = OEt, Y = H   (H$_2$L^4) (4)
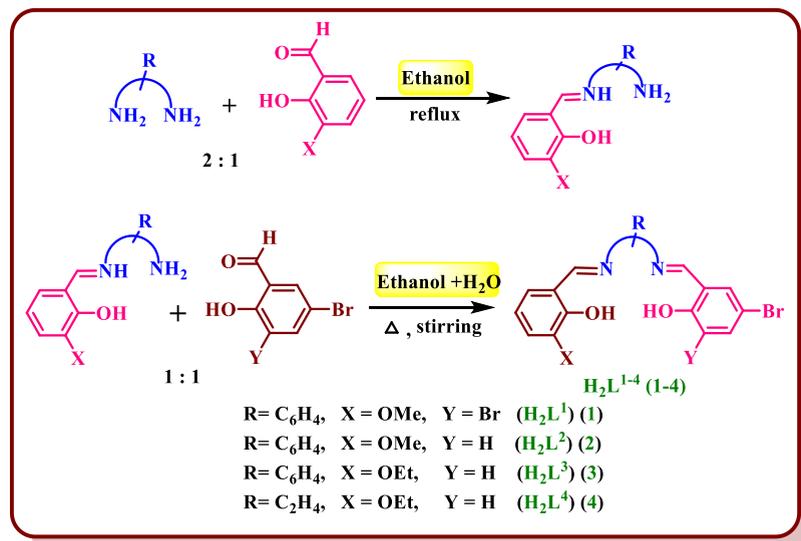
could therefore be highly crucial for the optimization and modification of catalytic systems.[79]

Until now, Ni−salen/Ni−unsymmetrical salen-based complexes have not been widely studied as catalysts as compared to their Mn, Cr, Co, or other similar transition metal counterparts. Only a few reports are present on Ni−salen complexes as catalysts mainly in olefin epoxidation and phenol oxidation reactions.[72,73,80−82] Many well-developed Ni-catalyzed multicomponent reactions are also reported for the synthesis of olefins,[83,84] allylic amines,[85] and some heterocyclic molecules,[86] where Ni-metal salts are used as a catalyst, but Ni-coordination complexes as catalysts in organic transformation are still scarcely developed.[74,87] Moreover, until now, pyran derivatives have also not been synthesized using Ni-based catalysts. Therefore, in light of the catalytic significance of Ni and metal-based unsymmetrical salen ligands, to our knowledge, this may be the first time we have reported any Ni−unsymmetrical salen-catalyzed MCRs that synthesize 2-amino-3-cyano-4H-pyran (ACP) derivatives. In this report, we have introduced four new Ni−unsymmetrical salen complexes [NiL$^{1-4}$] (5−8) and characterized them thoroughly along with solving the single-crystal X-ray diffraction (XRD) structures of 5, 6, and 8. The complexes were used as catalysts for one-pot MCRs for the efficient synthesis of ACP derivatives (using reagents 1,3-dicarbonyls, malononitrile, and benzaldehyde or its derivatives) in the ethanol medium, which resulted in up to 98% yield within 1 h reaction time.

■ EXPERIMENTAL SECTION

Materials and Methods. All of the chemicals were reagent-grade, purchased from standard sources, and used as received without further purification.

IR spectra and UV−vis spectra were recorded with a Perkin−Elmer Spectrum RXI and a Lamda25 Perkin−Elmer spectrometer, respectively. NMR spectra were recorded with a Bruker UltraShield 400 MHz spectrometer at 298 K room temperature using SiMe4 as an internal standard. All NMR (^{1}H and ^{13}C) spectra of catalytic products were recorded at room temperature in deuterated dimethyl sulfoxide (DMSO) solvent using a JEOL ECZ-R 500 MHz spectrometer. Further, more details are discussed in the Supporting Information.
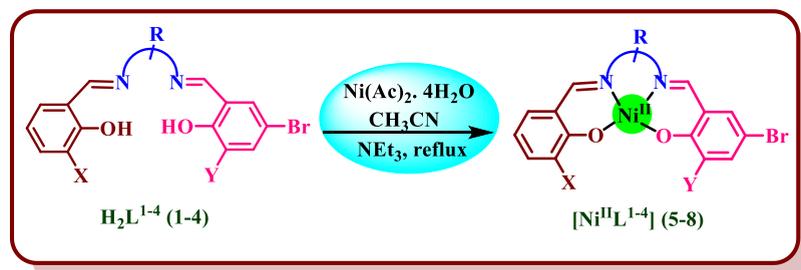
Synthetic Procedure of Unsymmetrical Salen Ligands (H$_2$L$^{1-4}$) (1−4). The unsymmetrical salen ligands were prepared in the following two steps:[88] In the first step, half a unit of the salen ligand was synthesized by the reaction of 2-hydroxy-3-methoxy salicylaldehyde or 2-hydroxy-3-ethoxy salicylaldehyde with corresponding diamine (1,2-phenylenediamine or 1,2-ethylenediamine) in a 1:2 ratio in ethanol solution under reflux conditions for 4 h.[89] The resulting half units of salen ligands were of dark orange color and were processed by filtering, washing with ethanol, and drying on fused CaCl$_2$. All half-unit ligands were produced in good yields, and their purity was determined by using several spectroscopic techniques. In the second step, these compounds further acted as precursors for the synthesis of unsymmetrical salen ligands. The half unit of the salen ligand reacted with their corresponding aldehydes (3,5-dibromo salicylaldehyde and 5-bromo salicylaldehyde) in a 1:1 ratio in the mixture of ethanol and water solvents at 55−60 °C for 3 h under both stirring and heating conditions (Scheme 1).[90] The resulting unsymmetrical salen ligands, [H$_2$L$^{1-4}$], were orange-yellow in color and were filtered, washed with ethanol, and dried over fused CaCl$_2$. All of the ligands, [H$_2$L$^{1-4}$] (1−4), were obtained in good yields. Finally, the purity of the ligands was analyzed through elemental analysis, IR, and NMR (^{1}H and ^{13}C) spectroscopy.

2,4-Dibromo-6-((E)-((2-(((E)-2-hydroxy-3-methoxybenzylidene)amino)phenyl)imino)methyl)phenol (H$_2$L^1) (1). Yield: 65%. MP: 169.1 °C. Anal. Calcd for C$_{21}$H$_{16}$Br$_2$N$_2$O$_3$: C, 50.03; H, 3.20; N, 5.56. Found C, 50.14; H, 3.32; N, 5.57. IR (KBr pellet, cm^{-1}): 3155 ν(O−H), 3152 ν(O−H), 1610 ν(C═N), 1596 ν(C═N). ^{1}H NMR (400 MHz, CDCl$_3$, ppm): δ 13.21 (s, 1H, OH), 13.06 (s, 1H, OH), 8.67 (s, 1H, CH), 8.55 (s, 1H, CH), 7.80−6.92 (m, 9H, aromatic), 3.94 (t, 3H, OCH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$, ppm): 163.68, 163.65, 157.66, 157.62, 141.19, 141.11, 138.30, 138.25, 134.69, 134.66, 129.17, 129.15, 121.80, 121.75, 120.62, 120.58, 112.26, 112.23, 110.08, 110.05, 56.35.

4-Bromo-2-((E)-((2-(((E)-2-hydroxy-3-methoxybenzylidene)amino)phenyl)imino)methyl)phenol (H$_2$L^2) (2). Yield: 71%. MP: 156.6 °C. Anal. Calcd for C$_{21}$H$_{17}$BrN$_2$O$_3$: C, 59.31; H, 4.03; N, 6.59. Found C, 59.50; H, 4.18; N, 6.36. IR (KBr pellet, cm^{-1}): 3153 ν(O−H); 3149

Scheme 2. Schematic Representation of the Structure of Ni−(Unsymmetrical Salen) Complexes [NiL$^{1-4}$] (5−8) Reported in This Work

ν(O−H), 1612 ν(C=N), 1583 ν(C=N). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 13.20 (s, 1H, OH), 13.06 (s, 1H, OH), 8.65 (s, 1H, CH), 8.58 (s, 1H, CH), 7.53−6.88 (m, 10H, aromatic), 3.94 (t, 3H, OCH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 163.68, 163.65, 157.66, 157.62, 141.19, 138.30, 138.25, 135.66, 134.69, 134.66, 129.17, 129.15, 121.80, 121.75, 120.62, 120.58, 112.26, 112.23, 110.08, 110.05, 56.35.

4-Bromo-2-((E)-((2-(((E)-3-ethoxy-2-hydroxybenzylidene)-amino)phenyl)imino)methyl)phenol (H$_2$L^3) (3). Yield: 67%. MP: 125.7 °C. Anal. Calcd for C$_{22}$H$_{19}$BrN$_2$O$_3$: C, 60.15; H, 4.36; N, 6.38. Found C, 60.36; H, 4.52; N, 6.44. IR (KBr pellet, cm^{-1}): 3165 ν(O−H), 3158 ν(O−H), 1612 ν(C=N), 1589 ν(C=N). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 13.12 (s, 1H, OH), 13.06 (s, 1H, OH), 8.64 (s, 1H, CH), 8.59 (s, 1H, CH), 7.53−6.86 (m, 10H, aromatic), 4.18−4.13 (q, 2H, −OCH$_2$), 1.51−1.46 (t, 3H, −OCH$_2$CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 164.8, 164.6, 156.6, 156.3, 142.4, 142.2, 138.3, 138.1, 134.5, 134.3, 129.17, 129. 14, 121.56, 121.54, 120.51, 120.48, 112.4, 112.1, 110.5, 110.34, 62.51, 15.68.

4-Bromo-2-((E)-((2-(((E)-2-hydroxy-3-methoxybenzylidene)amino)ethyl)imino)methyl)phenol (H$_2$L^4) (4). Yield: 69%. MP: 109.3 °C. Anal. Calcd for C$_{18}$H$_{19}$BrN$_2$O$_3$: C, 55.26; H, 4.89; N, 7.16. Found C, 55.27; H, 4.82; N, 7.14. IR (KBr pellet, cm^{-1}): 3135 ν(O−H), 3132 ν(O−H), 1632 ν(C=N), 1595 ν(C=N). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 13.65 (s, 1H, OH), 13.18 (s, 1H, OH), 8.35 (s, 1H, CH), 8.31 (s, 1H, CH), 7.41−6.76 (m, 6H, aromatic), 4.15−4.09 (q, 2H, −OCH$_2$), 3.98−3.96 (t, 4H, −NCH$_2$CH$_2$), 1.51−1.48 (t, 3H, −OCH$_2$CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 162.33, 162.31, 155.62, 147.67, 143.51, 135.56, 132.11, 125.26, 125.24, 123.58, 118.31, 118.28, 116.54, 110.87, 62.51, 56.89, 48. 55, 15.31.

General Synthetic Procedure for the Synthesis of Nickel(II)−(Unsymmetrical Salen) Complexes (5−8). *[NiL^1] (5).* This complex was synthesized by refluxing H$_2$L^1 (1 mmol) in 20 mL of acetonitrile. NEt$_3$ (2−3 drops) was added to the reaction mixture to favor the deprotonation of the ligand. Finally, Ni(Ac)$_2$·4H$_2$O (1 mmol) was added to the reaction. The reaction continued for 6 h, and after that, a deep red color compound was obtained from the reaction mixture. The compound was further crystallized in an acetonitrile and chloroform mixture to get red color suitable SC-XRD quality crystals. Yield: 51%. Anal. Calcd for C$_{22}$H$_{17}$Br$_2$N$_2$NiO$_3$: C, 45.88; H, 2.98; N, 4.86. Found C, 45.89; H, 2.88; N, 4.90. IR (KBr pellet, cm^{-1}): 1606 ν(C=N); 1589 ν(C=N). UV−vis (DMSO) [λ_{max}, nm (ε, M^{-1} cm^{-1})]: 476 (32,400), 440 (35,350), 380 (73,100). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.30 (s, 1H, N=CH), 8.21 (s, 1H, N=CH), 7.73−6.64 (m, 9H, aromatic), 3.87 (s, 3H, OCH$_3$).

[NiL^2] (6). The synthesis of 6 also followed a similar reaction condition as 5. Here, the H$_2$L^2 (1 mmol) ligand was used with nickel salt. Here also, a red color crystalline compound was collected from the reaction mixture, which was further crystallized with acetonitrile and chloroform to get suitable single crystals. Yield: 53%. Anal. Calcd for C$_{22}$H$_{18}$BrN$_2$NiO$_3$: C, 53.17; H, 3.65; N, 5.64. Found C, 53.29; H, 3.46; N, 5.68. IR (KBr pellet, cm^{-1}): 1607 ν(C=N); 1576 ν(C=N). UV−vis (DMSO) [λ_{max}, nm (ε, M^{-1} cm^{-1})]: 486 (18,250), 378 (60,000). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.14 (s, 1H, N=CH); 9.08 (s, 1H, N=CH); 8.18−6.58 (m, 10H, aromatic); 3.75 (s, 3H, OCH$_3$).

[NiL^3] (7). The synthesis of complex 7 also followed the same reaction state as 5 with ligand H$_2$L^3 (1 mmol). However, here, the red color XRD quality crystals were formed by recrystallization with DMSO. Yield: 62%. Anal. Calcd for C$_{23}$H$_{20}$BrN$_2$NiO$_3$: C, 54.06; H, 3.95; N, 5.48. Found C, 54.11; H, 3.71; N, 5.33. IR (KBr pellet, cm^{-1}): 1606 ν(C=N); 1564 ν(C=N). UV−vis (DMSO) [λ_{max}, nm (ε, M^{-1} cm^{-1})]: 483 (32,200), 378 (1,03,600). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.30 (s, 1H, N=CH); 8.22 (s, 1H, N=CH); 7.74−6.60 (m, 10H, aromatic); 4.11−4.06 (q, 2H, OCH$_2$); 0.92−0.88 (t, 3H, OCH$_2$CH$_3$).

[NiL^4] (8). The synthetic procedure of complex 8 was also the same as 5 with H$_2$L^4 (1 mmol). After 6 h of reaction, the solution of the filtrate was cleaned. So, it was kept for 3−4 days to get block-shaped orange color XRD quality single crystals. Yield: 59%. Anal. Calcd for C$_{19}$H$_{20}$BrN$_2$NiO$_3$: C, 49.29; H, 4.35; N, 6.05. Found C, 49.47; H, 4.33; N, 6.15. IR (KBr pellet, cm^{-1}): 1622 ν(C=N); 1586 ν(C=N). UV−vis (DMSO) [λ_{max}, nm (ε, M^{-1} cm^{-1})]: 445 (17,100), 415 (30,300), 347 (45,500). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.93 (s, 1H, N=CH); 7.89 (s, 1H, N=CH); 7.49−6.41 (m, 6H, aromatic); 3.99−3.94 (q, 2H, OCH$_2$); 1.30−1.27 (t, 3H, OCH$_2$CH$_3$).

General Synthetic Procedures for the Synthesis of 2-Amino-3-cyano-4H-pyran (ACP) Derivatives. The general procedure for the synthesis of ACPs is presented as follows: a 50 mL round-bottom flask was charged with a Ni catalyst and different dicarbonyl (2.5 mmol), malononitrile (198 mg, 3 mmol), and aromatic aldehydes (3 mmol) in 5 mL of ethanol solvent. The reaction mixture was continuously stirred while refluxing in an oil bath. A white precipitate was formed within 15 min in the reaction mixture, and the reaction was continued for an hour to get the maximum yield. After the completion of the reaction, the reaction mixture was kept in the refrigerator for an hour to cool down. The obtained precipitate was then filtered through a Buchner funnel and washed with cold ethanol. A pure white powder product was obtained, which was dried overnight in an oven. The product was analyzed by
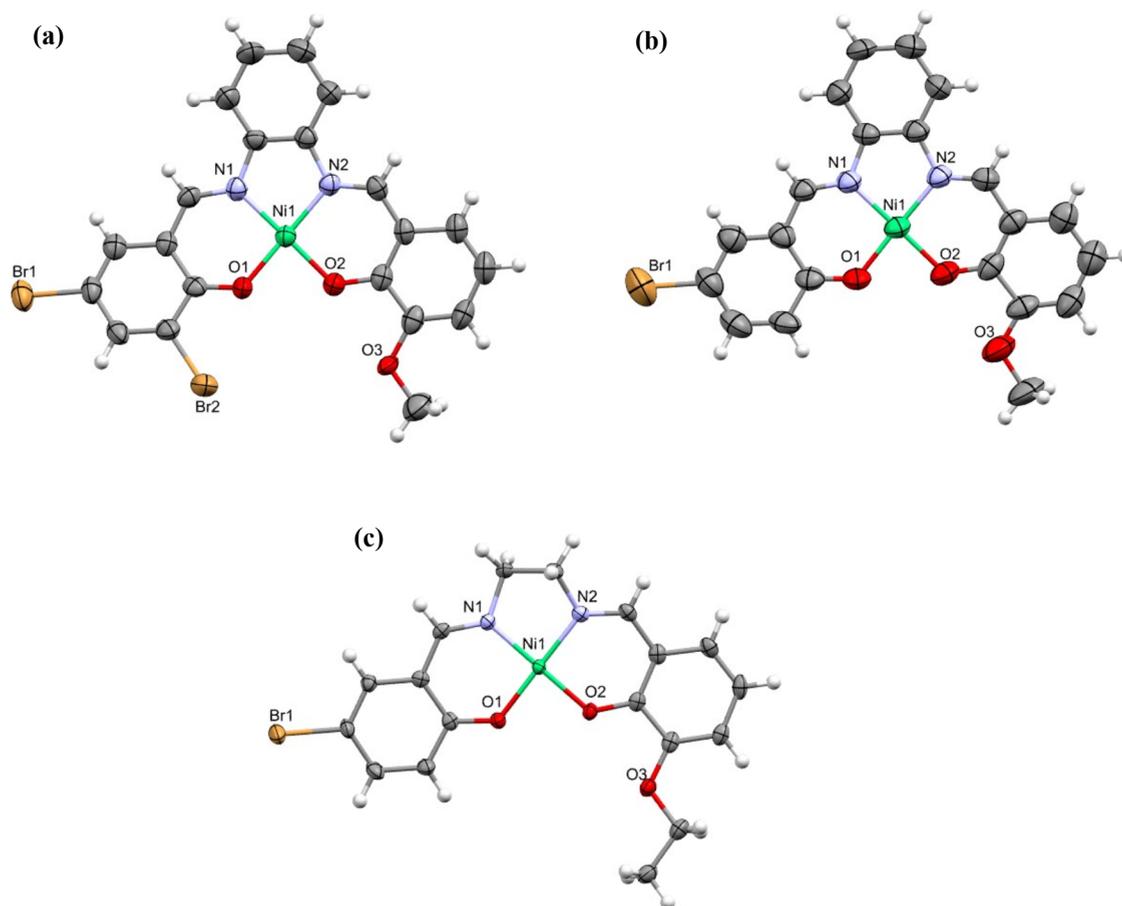
Figure 2. ORTEP representations with 50% probability thermal ellipsoids of $[NiL^1]$ (a), $[NiL^2]$ (b), and $[NiL^4]$ (c).

^{1}H NMR, ^{13}C NMR, and high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) characterization without any further purification.

Details on the characterization data have been included in the Supporting Information.

X-ray crystallographic analyses are discussed in the Supporting Information.

■ RESULTS AND DISCUSSION

Synthesis. In the present set of work, four Ni(II) complexes (**5−8**) were synthesized using corresponding unsymmetrical salen ligands ($H_2L^{1−4}$) and a metal precursor $(Ni(Ac)_2 \cdot 4H_2O)$ in acetonitrile solvent. NEt_3 was used as a base to accelerate the reaction. The synthetic routes of ligands and Ni complexes are depicted in Scheme 1 and 2, respectively. All of the complexes were collected in good yields and found to be completely air-stable, and the purity of the complexes was analyzed using elemental analysis. Furthermore, the solubility of the complexes was checked, indicating that **5−8** was soluble in almost all polar and nonpolar organic solvents. Moreover, the structural identity of **5−8** was characterized using HR-ESI-MS spectrometry, Fourier transform infrared spectroscopy (FTIR), NMR (^{1}H and ^{13}C), and UV−vis spectroscopic methods. Single crystals of all of the complexes were grown, which is described in the Experimental Section, and the structures of **5**, **6**, and **8** were further confirmed (solved) through the single-crystal X-ray diffraction method.

Characterization of 5−8. IR and UV−vis spectra of **5−8** (Figure S1) are discussed in the Supporting Information.

Single-Crystal XRD Description. The solid-state structures of complexes **5**, **6**, and **8** were solved using the SC-XRD technique. The thermal ellipsoid structures of these complexes, along with the numbering of the atoms, are shown in Figure 2. In addition, the crystallographic parameters and selected bond distances and angles are depicted in Tables 1 and S1, respectively. All three complexes (**5**, **6**, and **8**) are present in the monoclinic crystal system having the space group $\bar{P}2ybc$. The structures shown in Figure 2 indicate that the N_2O_2 donor set of atoms binds the nickel center in a distorted square-planar geometry in which nickel forms two six-membered rings and one five-membered ring with the donor atoms. The slightly distorted square-planner arrangements of the atoms are supported by the four O(1)−Ni−O(2), O(1)−Ni−N(1), O(2)−Ni−N(2), and N(1)−Ni−N(2) angles slightly diverge from 90° and present in the range of 83.7(2)−95.5(2). Also, the two angles between the trans atoms, O(1)−Ni−N(2) and O(2)−Ni−N(1), are in the range of 173.6(2)−179.0(2), which is very close to 180°. In addition, the Ni−O(1) and Ni−O(2) bond lengths are in the range of 1.857(4)−1.838(5) Å, which is nearly identical to the Ni−N(1) and Ni−N(2) bond distances (1.864(4)−1.848(3) Å). All of the bond distances are comparable to formerly reported Ni−N and Ni−O bonds.[72]

NMR Spectral Studies. NMR spectra were recorded for $H_2L^{1−4}$ and $[NiL^{1,3}]$ (**5** and **7**) in $CDCl_3$ and for $[NiL^{2,4}]$ (**6** and **8**) in DMSO-d_6, and the details of the assignment of peaks are given in the Experimental Section. Due to the unsymmetrical nature of ligands, two phenolic −OH peaks appeared

Table 1. Selected Bond Distances [Å] and Angles [deg] for 5, 6, and 8

	bond distances (Å)		
	5	**6**	**8**
Ni(1)−O(1)	1.842(3)	1.838(5)	1.850(3)
Ni(1)−O(2)	1.857(4)	1.856(5)	1.850(3)
Ni(1)−N(1)	1.864(4)	1.863(5)	1.855(4)
Ni(1)−N(2)	1.853(4)	1.850(5)	1.848(3)
O(1)−C(1)	1.289(7)	1.307(9)	1.303(6)
O(2)−C(20)	1.312(6)	1.305(9)	
O(2)−C(16)			1.307(6)
N(1)−C(7)	1.312(7)	1.295(8)	1.285(6)
N(1)−C(8)	1.429(7)	1.423(9)	1.481(5)
N(2)−C(13)	1.433(7)	1.439(8)	
N(2)−C(9)			1.471(6)
N(2)−C(14)	1.296(7)	1.298(8)	
N(2)−C(10)			1.291(7)
	bond angles (deg)		
O(1)−Ni(1)−N(1)	94.5(2)	95.5(2)	94.4(2)
O(2)−Ni(1)−N(2)	94.9(2)	94.8(2)	94.1(2)
O(1)−Ni(1)−O(2)	84.9(2)	83.7(2)	85.4(1)
N(1)−Ni(1)−N(2)	86.2(2)	86.0(2)	86.1(2)
O(2)−Ni(1)−N(1)	174.8(2)	177.0(2)	177.9(2)
O(1)−Ni(1)−N(2)	173.6(2)	177.6(2)	179.0(2)

in the range of 13.65−13.06 ppm. These peaks disappear after complexation.[91−93] Another characteristic peak of ligands appears in the 8.67−8.31 ppm range due to azomethine protons. However, in 5−8, the azomethine protons are shifted as compared to the ligands and appear in the range of 9.14−7.83 ppm, which is an indication of complex formation. In all of the ligands and complexes, the presence of two azomethine protons is also a sign of their unsymmetrical nature. Aromatic peaks appear in the range of 7.8−6.68 ppm. However, in the case of complexes, the range is 8.18−6.41 ppm. In 5 and 6, a singlet peak for the −OCH$_3$ group of the ligand appears at 3.87 and 3.75 ppm, respectively. However, in the case of 7 and 8, a quartet peak appears at about 4.11−3.94, while at around 1.30−0.88 ppm, a triplet peak appears for the −OCH$_2$CH$_3$ group of the ligand backbone. Details about the ^{1}H NMR of all of the ligands and complexes are explained in the Experimental Section, and the details about the ^{1}H NMR of H$_2$L$^{1−4}$ (1−4) and [NiL$^{1−4}$] (5−8) are given in Figures S2−S5.

Catalytic Activity Study. Based on the catalytic role of transitional metal complexes in multicomponent reactions,[62,63,65,66,68,94−98] for the first time in this work, Ni−unsymmetrical salen complexes are utilized as catalysts in a one-pot MCR for the efficient synthesis of ACP derivatives. Multicomponent reactions involving aromatic aldehydes, malononitrile, and dicarbonyl compounds have been carried out under different reaction conditions, with the best results

achieved within 1 h at 80 °C under an EtOH solvent medium (Scheme 3).[99−102]

Since the four Ni−unsymmetrical salen complexes are electronically in different environments, we had to obtain the most favorable reaction conditions to comprehend their suitability as catalysts. So, the optimized reaction condition is achieved by changing parameters such as catalyst amount, solvent, reaction time, and temperature of the reaction mixture, as represented in Figure 3 and Table S2. Complex 5 is selected as the representative catalyst and screening of the reaction conditions has been performed to find out the best result for this reaction. Fixed amounts of dimedone (350.45 mg, 2.5 mmol), malononitrile (198.18 mg, 3 mmol), and benzaldehyde (318.36 mg, 3 mmol) were treated with different solvent media and different amounts (i.e., 0.25, 0.50, and 0.75 mg) of complex 5 at different temperatures (i.e., r.t., 40, 60, and 80 °C). All of the systematic screening parameters and optimized reaction conditions for complex 1 to achieve maximum conversion (up to 94% yield) have been summarized in Table S2. From varying reaction conditions and parameters, it was found that 0.50 mg (0.00087 mmol) of Ni catalyst (1) loading in EtOH (5 mL) solvent at 80 °C for a reaction time of 1 h gave the maximum yield (up to 94%), and any further increase or decrease in any parameter did not show significant changes in the reaction (entry no. 14). We performed reactions in a variety of solvent media (e.g., EtOH, ACN, THF, CHCl$_3$, EtOAc, and aqueous EtOH) to find out the best solvent for the representative catalyst (5). Among all solvents used in this experiment, only ethanol showed excellent conversion toward the product (Table S2). A similar reaction was performed without a solvent medium, but no significant results were obtained. Catalytic reactions were performed at different temperatures (e.g., r.t., 40, 60, and 80 °C), and excellent yield was achieved only at 80 °C. Additionally, a few control experiments were carried out to gain a thorough understanding of the reaction mechanism. Therefore, a control experiment was conducted without a catalyst under optimized reaction conditions, which shows a 37% conversion rate in 2 h (Table S2 (entry no. 7)).

The one-pot multicomponent reactions for the synthesis of ACP and its derivatives were performed at our optimized reaction condition with the other Ni catalysts, i.e., complexes 6, 7, and 8. It was found that complex 5 shows excellent conversion (up to 94% yield) among all four complexes, and the resulting data are presented in Table 2. Considering the catalytic efficiency of these Ni complexes, the order of efficiency was found to be 5 > 7 > 6 > 8. A comparative study of these reactions was also performed with nickel salts and corresponding Ni−symmetrical salen (synthesized and characterized by NMR, Figure S6), and the results are shown in Table 2.

Under optimized reaction conditions, one-pot MCRs of different dicarbonyl, malononitrile, and aromatic aldehyde

Scheme 3. Synthetic Scheme for the One-Pot MCR for the Synthesis of ACP Derivatives
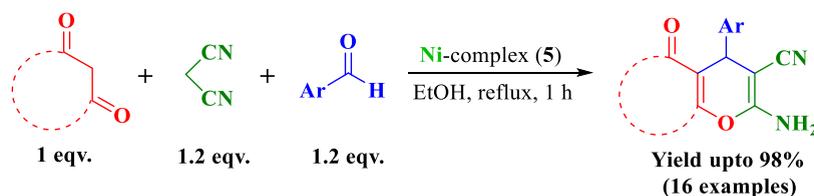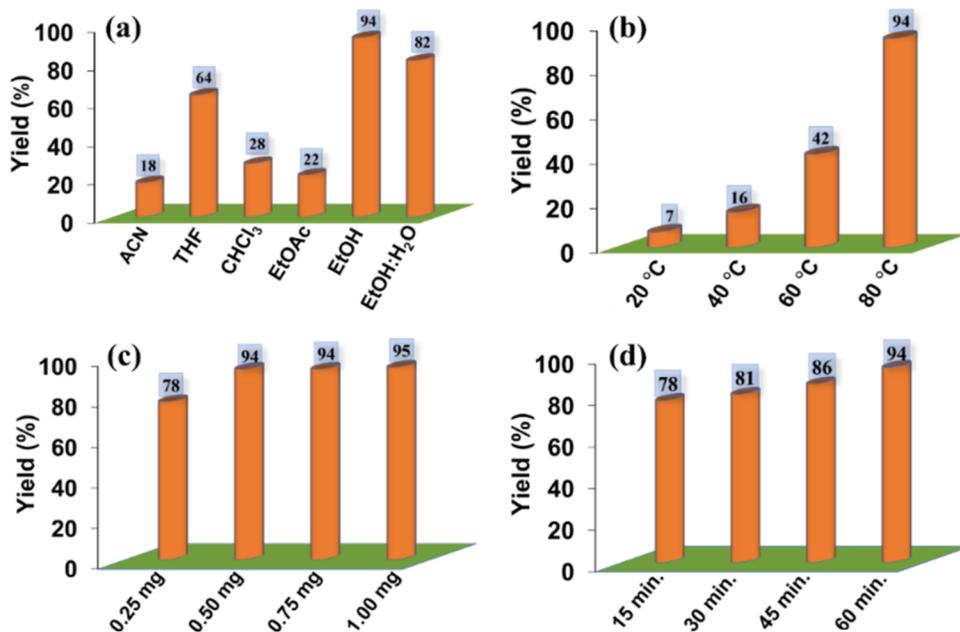
Figure 3. Effect of (a) solvent, (b) temperature, (c) catalyst amount, and (d) reaction time variation plot for the one-pot multicomponent reaction of ACP synthesis.

Table 2. One-Pot Multicomponent Reaction for the Efficient Synthesis of ACPs using Different Ni Complexes as Catalyst Precursors[a]

entry no.	catalyst [mg, μmol]	yield [%]	TOF [h^{-1}]
1	0.50 (0.87) (5)	94	2701
2	0.50 (1.01) (6)	88	2178
3	0.50 (0.97) (7)	91	2345
4	0.50 (1.08) (8)	85	1968
5	5 (21) [NiCl$_2$·6H$_2$O]	59	70
6	5 (20) [Ni(acac)$_2$·4H$_2$O]	62	78
7	0.50 (0.94) [symmetrical complex 5]	89	2367

[a]Reaction conditions: dimedone (350 mg, 2.5 mmol), malononitrile (198 mg, 3 mmol), benzaldehyde (318 mg, 3 mmol), solvent = EtOH (5 mL), reaction time = 1 h, and temperature = 80 °C. TOF (h^{-1}) = [number of moles of reactant consumed]/[(moles of catalyst) × (time of reaction in hours)]

derivatives were also tested (Table 3) by taking catalyst **5** as a representative. Table 3 demonstrates that in comparison to benzaldehyde, aromatic aldehyde with an electron-withdrawing group substituent exhibits better conversion (up to 98%), and an electron-donating group substituent exhibits similar or lower conversion. ^{1}H, ^{13}C NMR, and HR-ESI-MS data of all of the 16 derivatives of ACPs are given in Figures S7−S53.

Comparison of the Catalytic Efficiency of Ni Complexes (5−8) with the Catalytic Studies Reported in the Literature. The catalytic efficiency of the Ni complexes used in this work is compared with previously published work in the literature in terms of reaction conditions and isolated yield of the product, and the results are summarized in Table 4. All of the previously reported works in the literature have their own merits, but frequently, it is discovered that many of them require the use of a longer reaction time, a higher temperature, a higher catalyst amount, or the use of a precious catalyst. The Ni complexes reported in this work have shown competitive yield as compared to most of the previously reported work,

along with some additional advantages such as a lower amount of catalyst loading, higher TOF (h^{-1}) values, easy separation method, use of a green solvent, and no hazardous byproduct formation in this reaction. Although this work has many advantages, the homogeneous Ni complex prevented it from being reused.

Reactivity Study of Complex 5 with Multicomponent Reagents and the Possible Reaction Mechanism. Completing catalytic results of one-pot MCRs for efficient synthesis of ACPs encouraged finding out possible reaction mechanisms.[104] The interactions of metal complexes with multicomponent reagents were studied through UV−vis spectroscopy considering complex **5** as a representative catalyst. The details and possible interpretations of electronic spectra are discussed as follows: a solution of Ni complex **5** (0.002 g in 10 mL of DMSO, 3.49 × 10^{-4} M) was diluted five times (final concentration: 5.82 × 10^{-5} M). Then, the final concentration of the metal complex was treated with dropwise successive addition of a diluted benzaldehyde solution (0.010 g, 9.4 × 10^{-3} M) in DMSO (10 mL), and the resulting spectral changes observed in the UV−vis spectroscopy are shown in Figure 4a. After each successive addition of one drop of benzaldehyde solution, the intensity of the ligand to metal charge transfer (LMCT) band shown at 447 nm and the $n \rightarrow \pi^*$ transition band at 379 nm started to decrease slowly, while the $\pi \rightarrow \pi^*$ transition band at 279 nm increased sharply with no change in their positions. The interaction between benzaldehyde and the nickel metal center is indicated by a slight decrease in the LMCT band and the formation of an isosbestic point at 355 nm. The above-treated solution was further treated with one drop of successive addition of malononitrile solution (0.007 g, 10.6 × 10^{-3} M) dissolved in 10 mL of DMSO, which resulted in a slight increase of LMCT as well as the $n \rightarrow \pi^*$ band, but interestingly, $\pi \rightarrow \pi^*$ bands sharply shifted toward the right from 302 to 336 nm (red shift), as shown in Figure 4b. These changes are possibly due to the interaction of the metal center with the C ≡ N bond of malononitrile and the formation of a conjugated double bond

Table 3. Substrate Scope for the One-Pot MCR Using Different Dicarbonyl, Malononitrile, and Aromatic Aldehyde Derivatives Under Optimized Reaction Conditions with the Representative Catalyst (5)[a]

Sl. No.	Substrate component	Product	Yield [%]	Melting point (°C) Observed	Melting point (°C) Reported	TOF (h⁻¹)
[a]1		(1a)	94	224–226	225–227[99]	2701
2		(1b)	95	212–214	213–214[99]	2729
3		(1c)	89	198–200	197–199[99]	2557
4		(1d)	98	185–187	184–186[99]	2815
5		(1e)	91	202–204	204–205[100]	2614
6		(1f)	97	206–208	207–209[101]	2787
7		(1g)	88	224–226	226–228[102]	2528
8		(1h)	83	262–264	266–268[99]	2384

Table 3. continued

Sl. No.	Substrate component	Product	Yield [%]	Melting point (°C) Observed	Melting point (°C) Reported	TOF (h⁻¹)
9		(2a)	95	200-202	-	2729
10		(2b)	89	300-302	-	2557
11		(3a)	92	230-232	229-231[103]	2643
12		(3b)	97	233-235	235-237[103]	2787
13		(3c)	91	162-164	160-162[104]	2614
14		(3d)	96	224-226	225-227[99]	2758
15		(3e)	87	256-258	258-260[103]	2499
16		(3f)	88	190-192	190-192[103]	2528

[a]Optimized reaction conditions: dimedone (350 mg, 2.5 mmol), malononitrile (198 mg, 3 mmol), benzaldehyde (318 mg, 3 mmol), solvent = EtOH (5 mL), reaction time = 1 h, and temperature = 80 °C. TOF (h⁻¹) = [number of moles of reactant consumed]/[(moles of catalyst) × (time of reaction in hours)].

(C=C) of intermediate I (see in Scheme 4), which was also isolated and characterized by ¹H and ¹³C NMR spectroscopy (see in Figures S54 and S55). The above solution was further treated with dropwise successive addition of dimedone solution (0.015 g, 10.71 × 10⁻³ M) dissolved in 10 mL of DMSO. After each drop addition of dimedone, it was observed that there was again a slight decrease in the LMCT band, but interestingly, the $n \rightarrow \pi^*$ band started to decrease slightly, and

Table 4. Comparison of the Catalytic Efficiency of Ni Complexes with the Catalytic Studies Reported in the Literature

entry no.	catalyst[a] and conditions	reaction time (min)	yield (%)	refs
1	THEIC-SBA-15 (15 mg)/water (5 mL)/reflux	7	93	29
2	urea (10 mol %)/EtOH·H$_2$O(1:1)/RT	300	91	30
3	TiO$_2$−CNTs (15 mol %)/water (5 mL)/80 °C	90	97	33
4	[Mo^{VI}O$_2$] complex 1 (0.15 mol %)/EtOH (10 mL)/reflux	30	91	36
5	[V^{IV}O]/[V^{V}O$_2$] complex (4 mg)/EtOH (10 mL)/reflux	30	94	38
6	TFE/reflux	300	90	40
7	KF−alumina (0.2 mmol)/EtOH (10 mL)/70 °C	120	90	41
8	nanozeolite CP (40 mg)/water (5 mL)/95 °C	35	95	43
9	MgO (200 mg)/H$_2$O−EtOH (4:1) 10 mL/reflux	25	94	103
10	Yb(PFO)$_3$ (5 mmol)/EtOH/60 °C	300	90	107
11	(γ-Fe$_2$O$_3$-Im-Py)$_2$WO$_4$ (5 mol %)/solvent free/90 °C	90	95	108
12	2% Ce−V/SiO$_2$ (30 mg)/EtOH/RT	60	95	109
13	VO$_2$(L)(NHEt$_3$) (10 mol %)/MeCN/50 °C	45	97	110
14	**Ni complex 5 (0.03 mol %)/EtOH/reflux**	**60**	**94**	**this work**

[a]THEIC = 1,3,5-tris(2-hydroxyethyl)isocyanurate; SBA = silica-based mesoporous; TFE = trifluoroethylene; CP = clinoptilolite; PFO = perfluorooctanoate; Im = imidazolium moieties.

bands due to $\pi \rightarrow \pi^*$ transition showed a sharp blue shift and shifted from 337 to 306 nm (see in Figure 4c). These changes suggest that dimedone also interacted with the metal center and the blue shift band due to $\pi \rightarrow \pi^*$ transition, suggesting the consumption of malononitrile in the reaction mixture and formation of the desired product through the mentioned possible mechanism (Scheme 4).

Plausible Reaction Mechanism for Ni-Catalyzed One-Pot MCRs for the Efficient Synthesis of ACPs. A plausible reaction mechanism is sketched in Scheme 4. At first, it was suggested that coordination with the catalysts' nickel metal center would activate the carbonyl group of aromatic aldehydes. The next step involved the Knoevenagel condensation reaction, which produced intermediate **I** by reacting malononitrile with activated aldehyde. A similar coordination

of the 1,3-dicarbonyl compound with the Ni-metal center of the catalyst resulted in increased nucleophilicity. The reaction of the 1,3-dicarbonyl compound with intermediate **I** via the Michael addition reaction led to the formation of intermediate **II**, which transformed into intermediate **III** during tautomerism. The intramolecular rearrangement, coordination, and activation of intermediate **III** with the catalyst led to the formation of intermediate **IV**. Finally, ACPs were formed from intermediate **IV** via a hydrogen atom rearrangement reaction. Similar pathways of the reaction were also suggested by Magyar et al.,[105] Ebrahimiasl et al.,[106] and Maurya et al.[36,38,94] for one-pot multicomponent reactions.

■ CONCLUSIONS

In summary, we have developed a straightforward, greener multicomponent approach for the efficient synthesis of biologically active ACPs taking Ni(II)−unsymmetrical salen complexes [NiL$^{1−4}$] (**5−8**) as catalysts for the first time under mild and simple conditions. A key advantage of this synthesis procedure is its high yield, the use of an environmentally safe solvent and reaction methodology, the simplicity of the experiment, the availability and affordability of starting materials, the ability to synthesize pyran derivatives on a large scale, and the short reaction time. From the comparison of results between these synthesized Ni(II) catalysts, it was found that the efficiency of catalytic performance follows the order **5 > 7 > 6 > 8**. So, various (a total of 16) 2-amino-3-cyano-4H-pyran derivatives were prepared using different 1,3-dicarbonyl, malononitrile, and aromatic aldehyde derivatives under optimized reaction conditions taking complex **5** as a representative catalyst. According to the results, under optimal reaction conditions, aromatic aldehyde with an electron-withdrawing group substituent exhibits better conversion (up to 98%), and aromatic aldehyde with an electron-donating group substituent exhibits similar or lower conversion compared to benzaldehyde.

Overall, this work offers a commanding alternative protocol (other than the existing one) for the efficient synthesis of this substantial class of heterocycle compounds using the abundantly accessible, easily synthesized, and cheap Ni catalyst system. As far as we know, this is the first report on a one-pot synthesis of any pyran derivative using a Ni metal-based complex as a catalyst. The current results provide a potential avenue for the application of Ni−unsymmetrical salen-based complexes as catalysts in a number of multicomponent
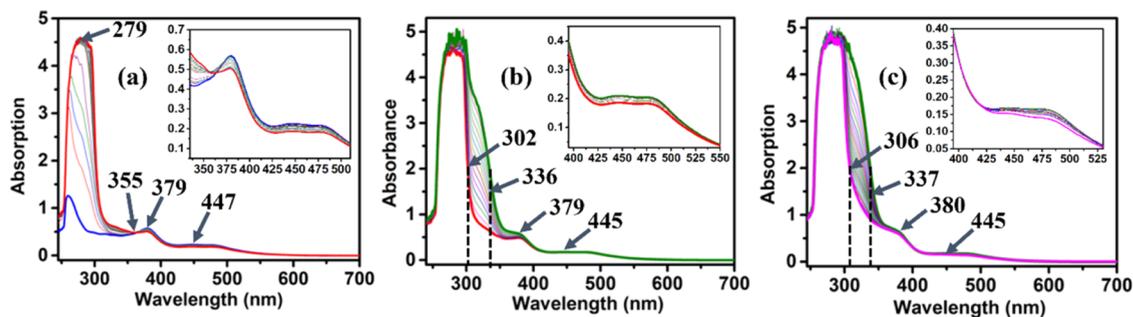

Figure 4. (a) UV−vis spectrum changes were noted following the dropwise addition, every 2 min, of a diluted 10 mL DMSO solution of complex **5** (5.82 × 10^{-5} M) containing benzaldehyde solution (9.4 × 10^{-3} M) dissolved in 10 mL of DMSO. (b) After adding a drop of dissolved malononitrile solution (10 mL of DMSO, 10.6 × 10^{-3} M) to the solution (a) above, every 2 min, spectral changes were noted. (c) After adding one drop of dimedone (10.71 × 10^{-3} M) to mixture solutions (a) and (b) above, respectively, every 2 min, spectral changes were recorded.

Scheme 4. Plausible Reaction Mechanism for the Ni-Catalyzed One-pot Multicomponent Reaction for the Synthesis of ACPs
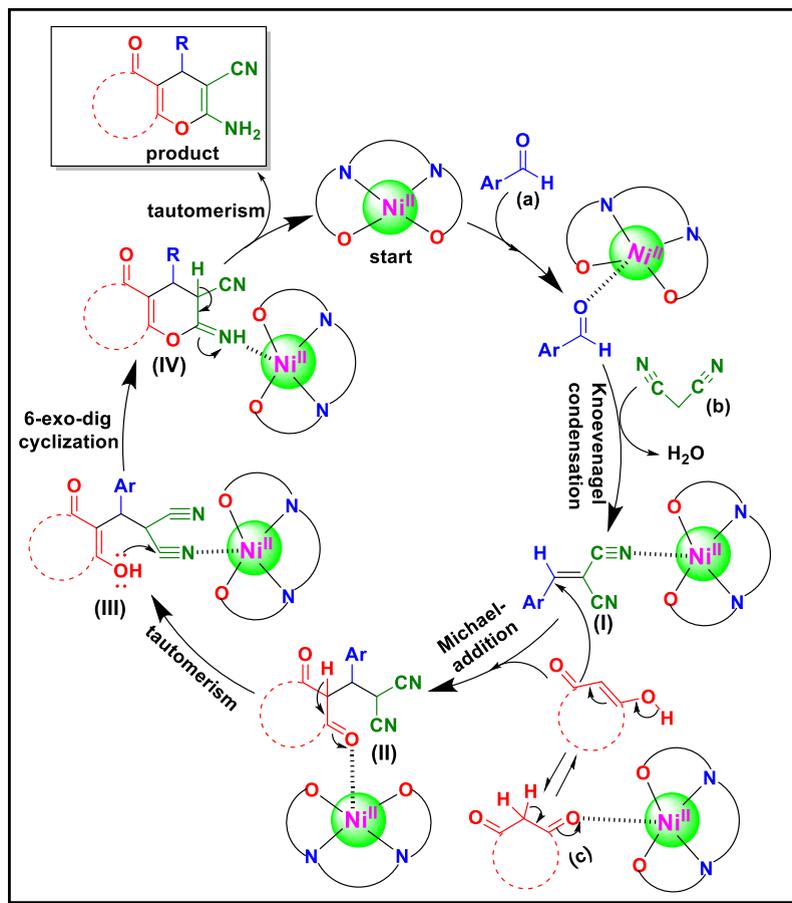
reactions in the near future. Research along these lines is in progress in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c03528.

> IR, UV−vis, and NMR data of H$_2$L$^{1-4}$, **5−8**, and all the catalytic products; HR-ESI-MS data of all of the catalytic products; and NMR data of intermediate species (PDF)
> Crystallographic data 1 (ZIP)
> Crystallographic data 2 (ZIP)

Accession Codes

CCDC-2263212 for **5**, CCDC-2263211 for **6**, and CCDC-2263206 for **8** contain the supplementary crystallographic data for this paper. Crystallographic data (excluding structure factor) can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [E-mail: deposit@ccdc.cam.ac.uk]

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Author Contributions

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Author Contributions

In manuscript preparation, all of the authors have given their input and given their approval for submission.

Notes

The authors declare no competing financial interest.

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