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Synthesis of Novel Diphenyl Ether-Based Bis-Heterocycles as Novel Hybrid Molecules via Michael and Other Cyclocondensation Reactions

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Cite This: *ACS Omega* 2024, 9, 4073−4084

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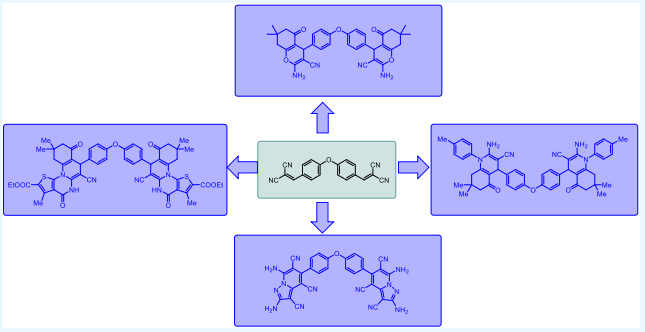
ABSTRACT: Molecular hybridization is a technique used in drug creation that involves combining the pharmacophoric moieties of multiple bioactive compounds to create a new hybrid molecule with better affinity and effectiveness. In this regard, we created unique hybrid molecules out of diphenyl ether-linked fused pyrans and other heterocycles. The Michael reaction of 4,4′-oxydibenzaldehyde with malononitrile and various active methylene derivatives, as well as enaminone derivatives, produced the matching bis-fused pyrans and fused pyridines, both connected to a diphenyl ether moiety. Furthermore, the acid-catalyzed reaction of 4,4′-oxydibenzaldehyde with dimedone or *β*-naphthol produced the corresponding new bis(hexahydro-1*H*-xanthene-1,8-dione) and bis(14*H*-dibenzo[*a*,*j*]xanthene). The processes by which the target products are formed were also examined.



INTRODUCTION

Multicomponent reactions (MCRs) provide an appealing, rapid, and effective means of obtaining synthetic organic molecules.[1−5] The Michael addition reaction is one of the most frequent MCRs for producing heterocycles via C−C bond formations. The effective use of a tandem Michael addition is observed in the complete synthesis of the antibacterial chemical claenone.[6] In this regard, Yamada et al.[6] were able to create a norbornane ring using two sequential Michael additions. Other reactions that employ the Michael reaction is the well-known Robinson annulation, in which the Michael addition happens as the initial step, followed by intramolecular aldol.[7]

Molecular hybridization is the process of integrating at least two pharmacophore fragments from separate bioactive molecules to create hybrids that outperform the original substances. The resultant molecule size, which is larger than the origin, typically contributes to increased lipophilicity. Hybridization may lead to the development of anticancer drugs that are both safer and more potent than those now available on the market.[8,9] Furthermore, due to their extraordinary lipophilicity, hydrophobicity, ability to penetrate cell walls, and resistance to degradation, diaryl ether substructures are important in various medications and recently discovered agrochemicals.[10,11] They have been discovered to have a variety of bioactivities, including antiviral, anticancer, antibacterial, *β*-glucuronidase enzyme inhibitory action, radical scavenging, cytotoxicity, antitubercular, and antitubulin activity.[12−16] Bis-heterocyclic compounds are among the popular scaffolds frequently found in drugs and pharmaceutically relevant substances because combining different heterocycle systems produces novel hybrid molecules that may be more biologically active than their separate components. There have been several reports of the antibacterial, anticancer, antiallergic, and other disease-fighting effects of bis-heterocycles.[17,18] Encouraged by the findings above and as part of our ongoing research interest in the synthesis of heterocycles and their bis-heterocyclic analogues,[19−52] we present the design and synthesis of novel hybrid molecules composed of diphenyl ether linked to various heterocyclic systems. In this context, we recently investigated the Hantzsch reaction for the manufacture of bis-dihydropyridine and their corresponding fused derivatives based on diphenyl ether, and their antibacterial activity against various bacterial strains was evaluated.[53] (Figure 1).

RESULTS AND DISCUSSION

In this study, 4,4′-oxydibenzaldehyde **3** was chosen as a precursor. It is prepared as described by Foyer et al.[54] via the reaction of the potassium salt of 4-hydroxybenzaldehyde **2** with 4-fluoro benzaldehyde **1** in DMF at reflux. The Michael addition

Received: November 15, 2023
Revised: December 21, 2023
Accepted: December 27, 2023
Published: January 5, 2024

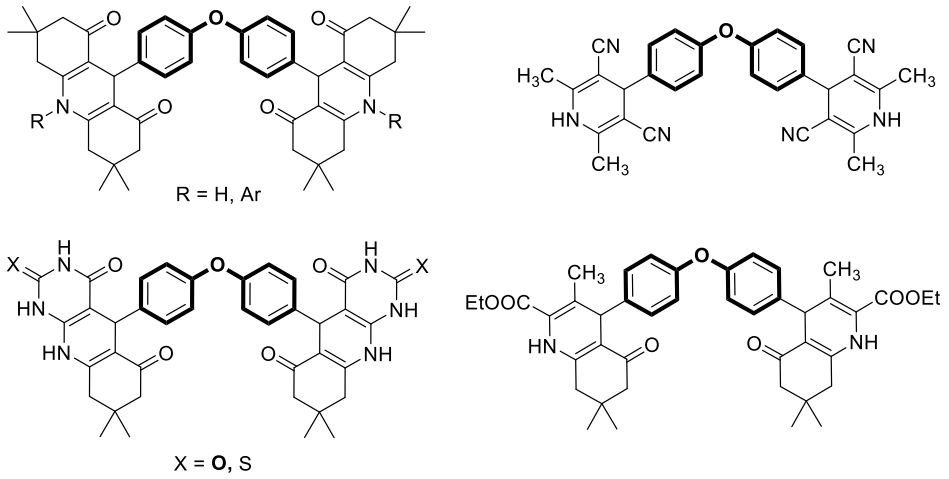
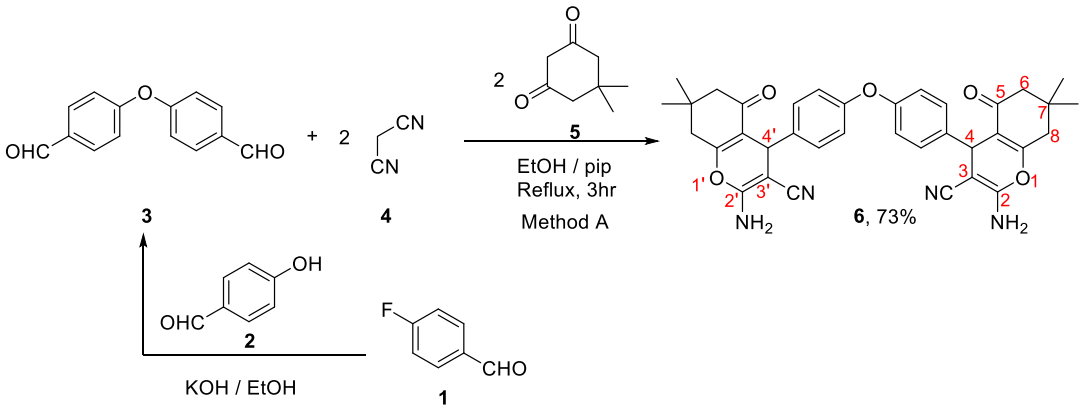
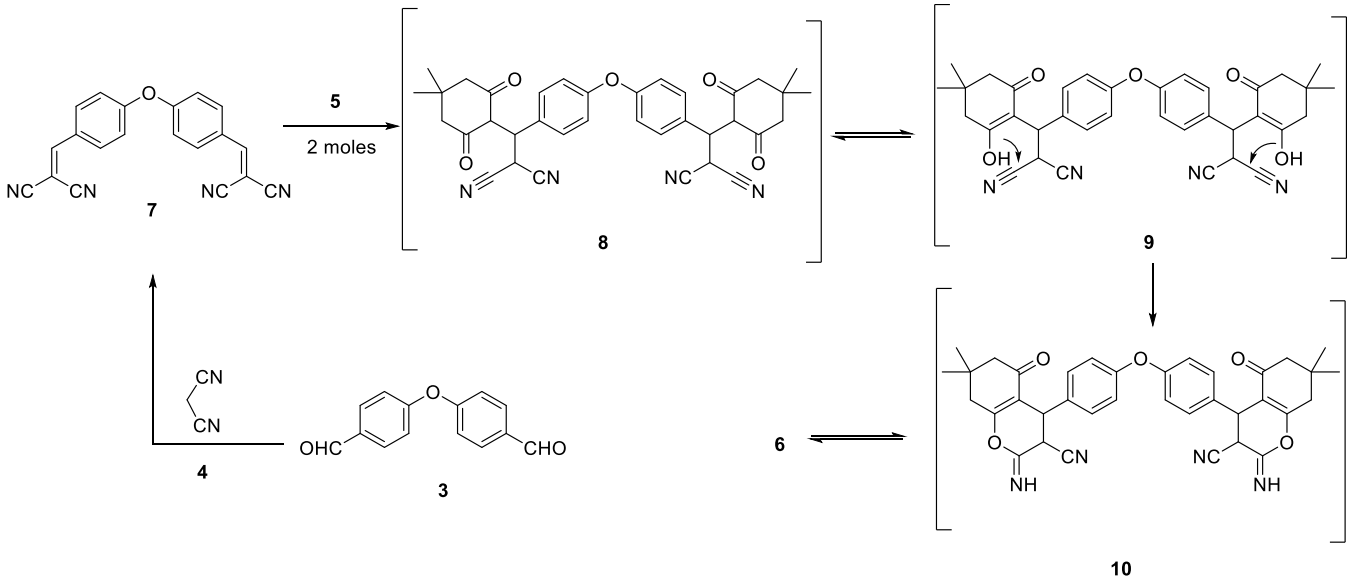


Figure 1. Some diphenyl ether-based bis-dihydropyridines.

Scheme 1. Synthesis of Bis(2-amino-tetrahydro-4*H*-chromene-3-carbonitrile) 6



Scheme 2. Plausible Mechanism for the Formation of 6



reaction of 4,4′-oxydibenzaldehyde with active methylene-containing reagents was then investigated. Thus, the reaction of 4,4′-oxydibenzaldehyde **3** with 2 mol equivalents of both malononitrile **4** and dimedone **5** in ethanol in the presence of piperidine as a basic catalyst afforded the bis(2-amino-tetrahydro-4*H*-chromene-3-carbonitrile) **6** linked to diphenyl ether (Scheme 1).

The structure of compound **6** was confirmed based on spectral analyses. Thus, the IR spectrum of compound **6** displayed bands at 3394, 3330, 2190, and 1676 cm^{-1}

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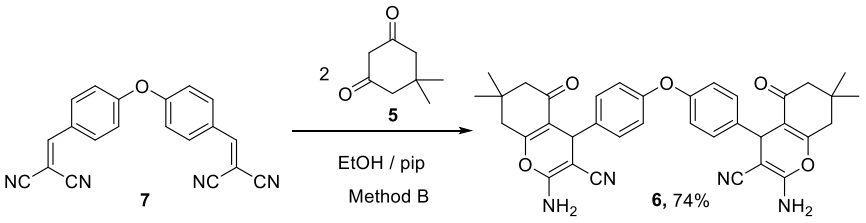
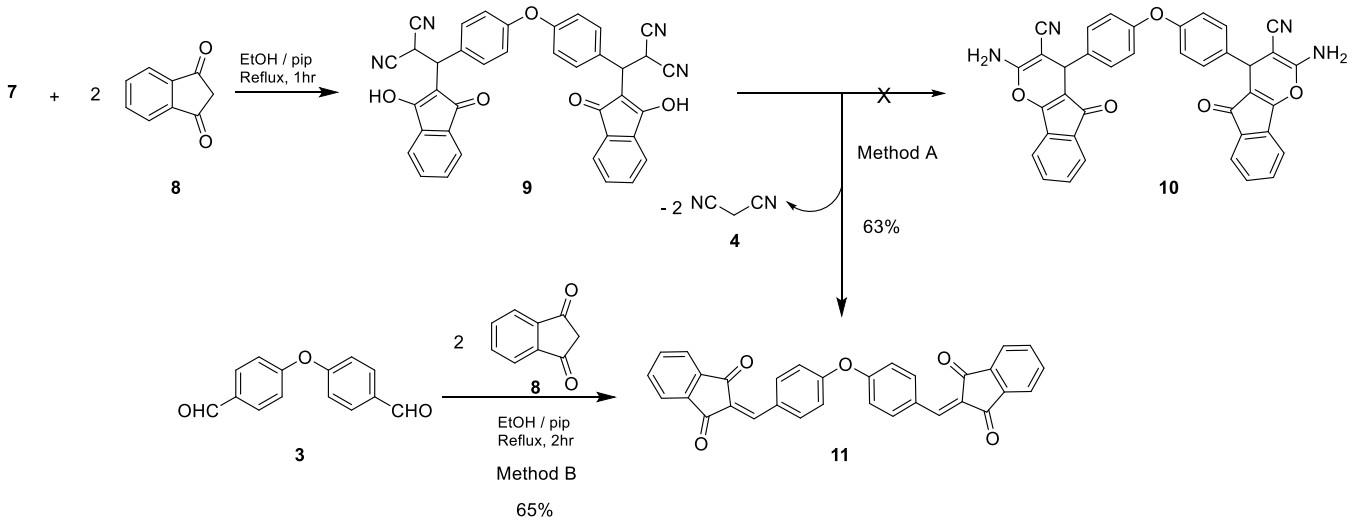
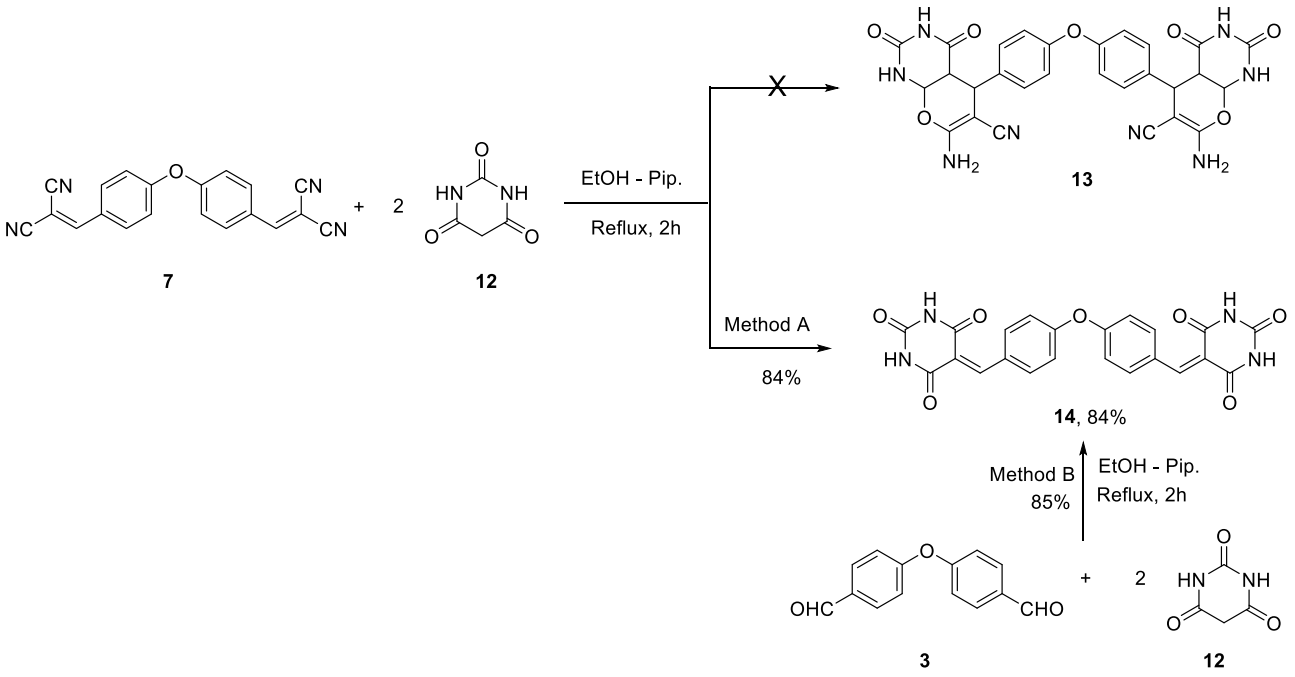
Scheme 3. Synthesis of 6 from Bis(methaneylylidene)dimalononitrile 7



Scheme 4. Synthesis of 2,2′-(Oxybis(4,1-phenylene))bis(methaneylylidene)bis(1*H*-indene-1,3-dione) 11



Scheme 5. Synthesis of Bis(methaneylylidene)bis(pyrimidine-2,4,6-trione) 14



characteristic of the NH, C═O, and cyano groups, respectively. The ^{1}H NMR spectrum of **6** showed two singlets at 0.96 and 1.03 ppm, corresponding to the four methyl groups. Besides, it revealed multiplets at 2.10−2.27 and 2.49−2.51 ppm for H6 and H8. The chromene-H4 was indicated as a singlet signal at 4.17. Moreover, it featured the amino group as a broad signal at 6.96 ppm. The aromatic protons appeared as two doublets at 6.88 and 7.12 with a coupling constant (J = 8.8 Hz). Additionally, the hypothesized structure was found to be supported by the ^{13}C NMR spectra of **6**, which had 16 signals corresponding to 16 carbon atoms. It displayed signals at 118.4 and 119.8 ppm characteristic for the two methyl and CN groups, respectively. Furthermore, the ^{13}C NMR spectrum of **6** revealed the C4 at 34.9 and the carbonyl group at 195.8.

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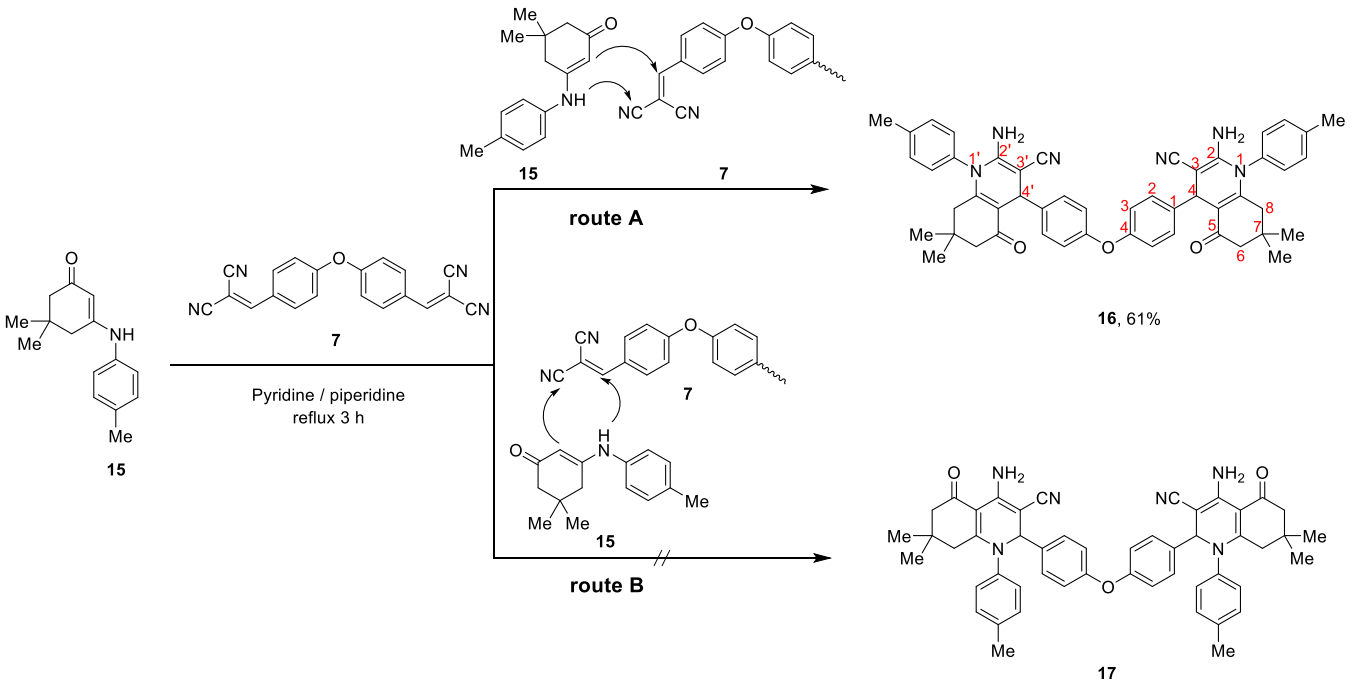
Scheme 6. Plausible Mechanism for the Formation of 16



The reaction begins with a Knoevenagel condensation of **3** with malononitrile **4** to produce 2,2′-((oxybis(4,1-phenylene))-bis(methaneylylidene))dimalononitrile **7**. The Michael addition reaction proceeds by first adding dimedone CH to the activated double bond in **7** to produce intermediate **8** that rearranges into **9**. The intermediate **9** cyclizes into **10** and finally tautomerizes to give **6** (Scheme 2).

We were able to isolate the Knoevenagel condensation product **7**, which can be considered evidence of this mechanism. Thus, bis(methaneylylidene)dimalononitrile **7** was produced in good yields by the 1 mol of 4,4′-oxydibenzaldehyde **3** with 2 mol of malononitrile **4** in ethanol in the presence of piperidine as a basic catalyst. The subsequent reaction of **7** with 2 mol of dimedone **5** in ethanol in the presence of piperidine yielded **6** in good yield (Scheme 3).

Otherwise, under the same reaction conditions, attempts to make bis-dihydroindeno[1,2-*b*]pyran-3-carbonitrile **10**, using 1,3-indandione **8** as a Michael donor, were unsuccessful. Alternatively, 2,2′-((oxybis(4,1-phenylene))bis-(methaneylylidene))bis(1*H*-indene-1,3-dione) **11** was obtained in an excellent yield as a sole product (Scheme 4). Presumably, the reaction starts with the formation of adduct **9**, which then decomposes to generate **11** by the removal of malononitrile. An identical sequence has already been documented.[55−60] The formation of compound **11** was verified by comparing its physical data with an authentic sample prepared from the reaction of 1 mol of 4,4′-oxydibenzaldehyde **3** with 2 mol equivalents of indanedione **8** in the presence of piperidine. The structure of compound **11** was verified based on IR and ^{1}H NMR spectra. Thus, the IR spectrum of compound **11** displayed bands at 1692 cm^{-1} characteristic of the C═O group. The ^{1}H NMR spectrum of **11** indicated the presence of a singlet signal at 7.84 ppm for the arylidene H.

Following a similar mechanism, the reaction of bis-(methaneylylidene)dimalononitrile **7** with barbituric acid **12** afforded bis(methaneylylidene)bis(pyrimidine-2,4,6-trione) **14** rather than bis(7-amino-2,4-dioxohexahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile) **13**. The physical data of compound **14** were compared to an authentic sample generated by reacting 1 mol of 4,4′-oxydibenzaldehyde **3** with 2 mol equivalents of barbituric acid **12** in the presence of piperidine (Scheme 5).

The Michael addition reaction of 5,5-dimethyl-3-(*p*-tolylamino)cyclohex-2-en-1-one **15** with bis-(methaneylylidene)dimalononitrile **7** was also studied. There are two probable regioisomers for the reaction product. The first possible isomer, bis(2-aminohexahydroquinoline-3-carbonitrile) **16** is formed by the initial addition of enamine CH of **15** to the *β*-carbon of the double bond in bis-(methaneylylidene)dimalononitrile **7**, followed by cyclization through the attack of the amine NH on the CN group (Scheme 6, route A). According to route B, the second plausible isomer, bis(4-aminohexahydroquinoline-3-carbonitrile) **17** is produced by the first nucleophilic attack of NH of **15** to the double bond in bis(methaneylylidene)dimalononitrile **7** and then cyclizing the compound through enamine C−H and CN groups (Scheme 6, route B). Even though ^{1}H and ^{13}C NMR simply could not distinguish between the two isomers, we addressed this issue without a doubt and assumed compound **16** to have the correct structure based on prior chemical elucidation[61−63] and HMBC spectroscopy[64] of certain related compounds. The mass spectrum of **16** showed a molecular ion peak at m/z = 780 [M$^+$]. The IR spectrum of compound **16** displayed bands at 3441, 3328, 2185, and 1685 cm^{-1} characteristic for the NH$_2$, C═O, and cyano groups, respectively. The ^{1}H NMR revealed a singlet at δ 4.46 for quinoline-*H*4 and a singlet at δ 5.25 for the amino group. The aromatic protons appeared as multiplets at δ 7.27−7.39. ^{13}C NMR spectrum of **16** displayed signals at 20.9, 26.4, and 118.5 ppm characteristic of the two methyl and CN groups, respectively. Furthermore, it revealed the C4 at 35.8 ppm and the carbonyl group at 195 ppm.

In a trial to provide chemical evidence to the former reaction (route 1), we extended our study to include the Michael addition reaction of bis(methaneylylidene)dimalononitrile **7**

https://doi.org/10.1021/acsomega.3c09081
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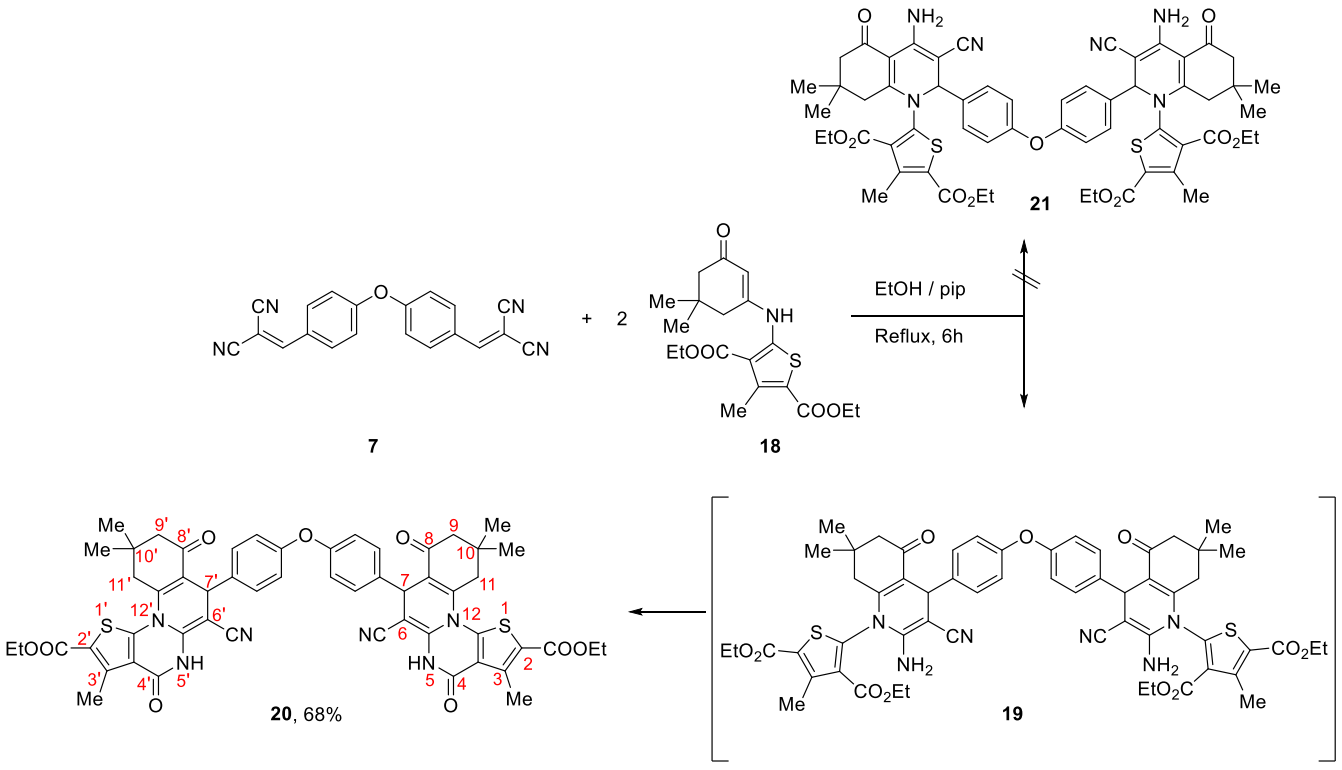
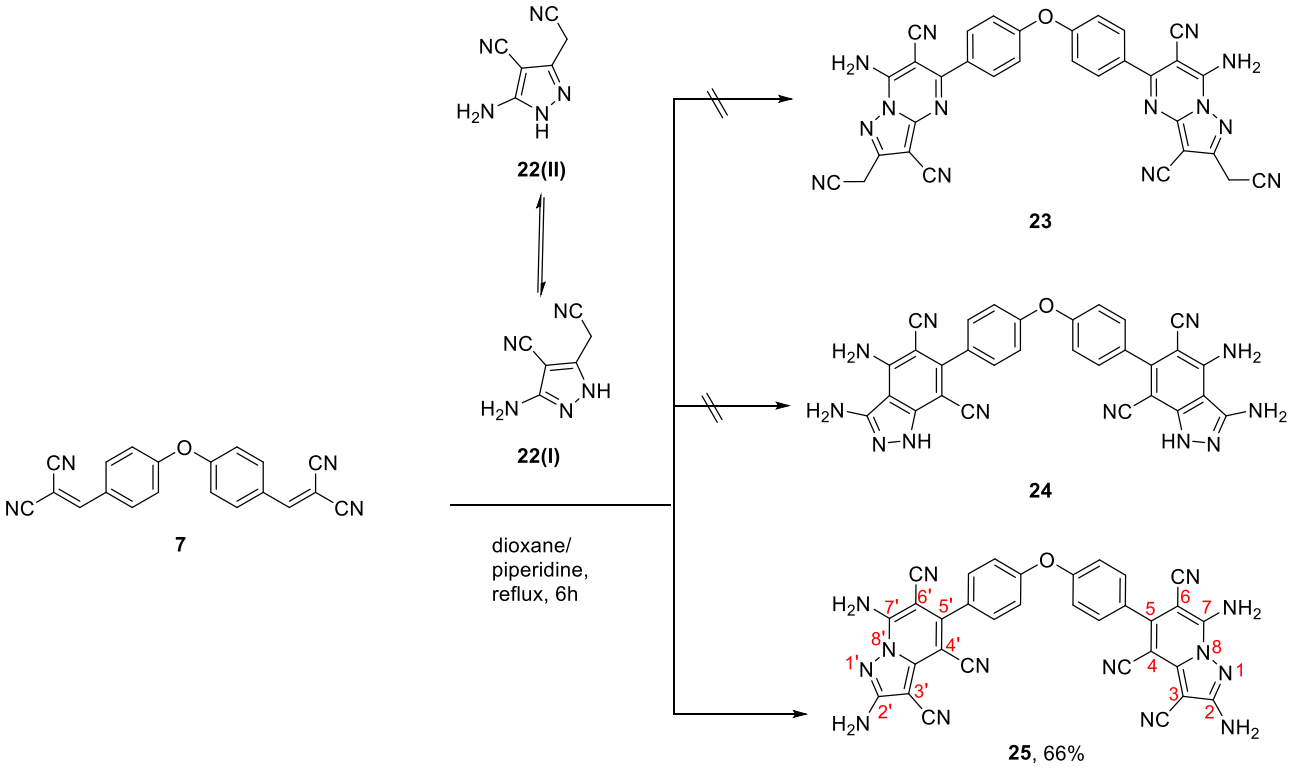
Scheme 7. Synthesis of Diethyl Bis(6-cyanohexahydro-4*H*-thieno[3′,2′:5,6]pyrimido[1,2-*a*]quinoline-2-carboxylate) 20



Scheme 8. Possible Products from the Reaction of Bis(methaneylylidene)dimalononitrile with 22



toward diethyl 5-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-amino)-3-methylthiophene-2,4-dicarboxylate **18**.[61] Interestingly, the process produced the tetracyclic diethyl bis(6-cyanohexahydro-4*H*-thieno[3′,2′:5,6]pyrimido[1,2-*a*]-quinoline-2-carboxylate) **20**. Presumably, the initially formed tetraethyl bis-5-(2-aminotetrahydroquinolin-1(4*H*)-yl)-3-methylthiophene-2,4-dicarboxylate **19**, underwent further cyclization to **20** through ethanol elimination (Scheme 7). It is worth noting that if **21** was the formed result of the reaction of **7** with **18**, then the tetracyclic system **20** could not be produced. It

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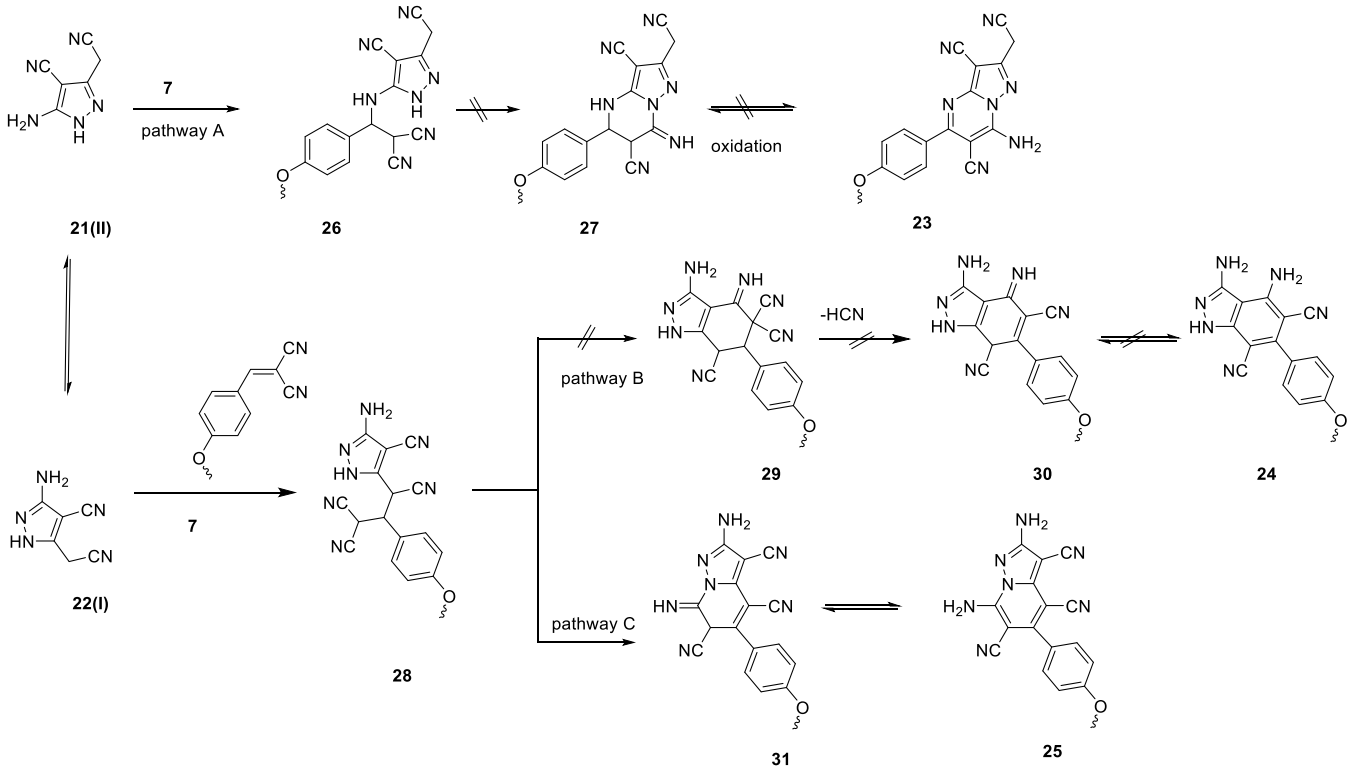
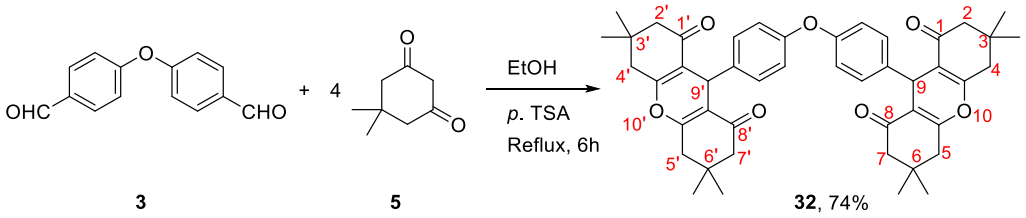
Scheme 9. Proposed Mechanistic Pathway for Compounds 23, 24, and 25



Scheme 10. Synthesis of Bis(hexahydro-1*H*-xanthene-1,8-dione) 32



should be emphasized that the thieno[3′,2′:5,6]pyrimido[1,2-*a*]quinoline ring system is not well-known in the literature, with only one example from our side.[61]

The constitution of compound **20** was verified based on spectral analysis. The mass spectrum of **20** showed a molecular ion peak as a base peak at *m*/*z* 988, corresponding to the loss of an ethanol molecule. The IR spectrum of compound **20** displayed bands at 3433 (NH) and 2198 cm^{-1} characteristic for the NH and CN groups, respectively. It also revealed two peaks for different CO groups at 1715 and 1662 cm^{-1}. The ^{1}H NMR also indicated a singlet signal at 4.60 ppm for H-7, in addition to a broad singlet signal at 11.55 ppm for the NH group. ^{1}H NMR also indicated the absence of one of the two EtOH protons, suggesting the cyclization of the amino group with the ester group of compound **19** to afford **20**. The ^{13}C NMR spectrum of **20** displayed signals at 24.8, 30.1, and 118.5 ppm characteristics for the two methyl and CN groups, respectively. Furthermore, it revealed the C7′ at 35.2 ppm and the carbonyl groups at 161.4 and 195.5 ppm.

Stimulated by the above results, the reactivity of bis-(methaneylylidene)dimalononitrile toward 5-amino-3-(cyano-methyl)-1*H*-pyrazole-4-carbonitrile **22** was also studied. The reaction of bis(methaneylylidene)dimalononitrile **7** with two equivalents 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **22** can theoretically afford one of three products, **23**, **24**, or **25** (Scheme 8).

Bis(7-amino-2-(cyanomethyl)pyrazolo[1,5-*a*]pyrimidine-3,6-dicarbonitrile) **23** can be obtained via the Michael addition of the compound **7** to the amino group of **22(II)**, followed by cyclization with the pyrazole-NH to give **23** via intermediates **26** and **27** (Scheme 9, pathway A). Bis(3,4-diamino-1*H*-indazole-5,7-dicarbonitrile) **24**, can be obtained through the Michael addition of the $-\underline{CH_2}CN$ group in compound **22(I)** to the double bond in **7** affording **28**. The cyano group at the pyrazole ring of compound **28** undergoes cyclization to give **29**. Subsequent elimination of HCN and aromatization produced **24** via intermediate **30** (Scheme 9, pathway B). Bis(4,1-phenylene)bis(2,7-diaminopyrazolo[1,5-*a*]pyridine-3,4,6-tricarbonitrile) **25** is produced through the cyclization of the pyrazole-NH of **28** via intermediate **31** (Scheme 9, pathway C).

Based on the ^{1}H NMR spectrum, which showed a no $-CH_2CN$ group in the range of 3−5 ppm, compound **23** was easily ruled out. Additionally, mass spectroscopy does not show that HCN has been removed, ruling out compound **24**. Furthermore, the ^{1}H NMR spectrum of **25** indicated the presence of two amino groups as two broad singlet signals at δ = 6.71 and 8.68 ppm. The aromatic protons appeared as two doublets at 7.27 and 7.64 ppm. Moreover, the ^{13}C NMR

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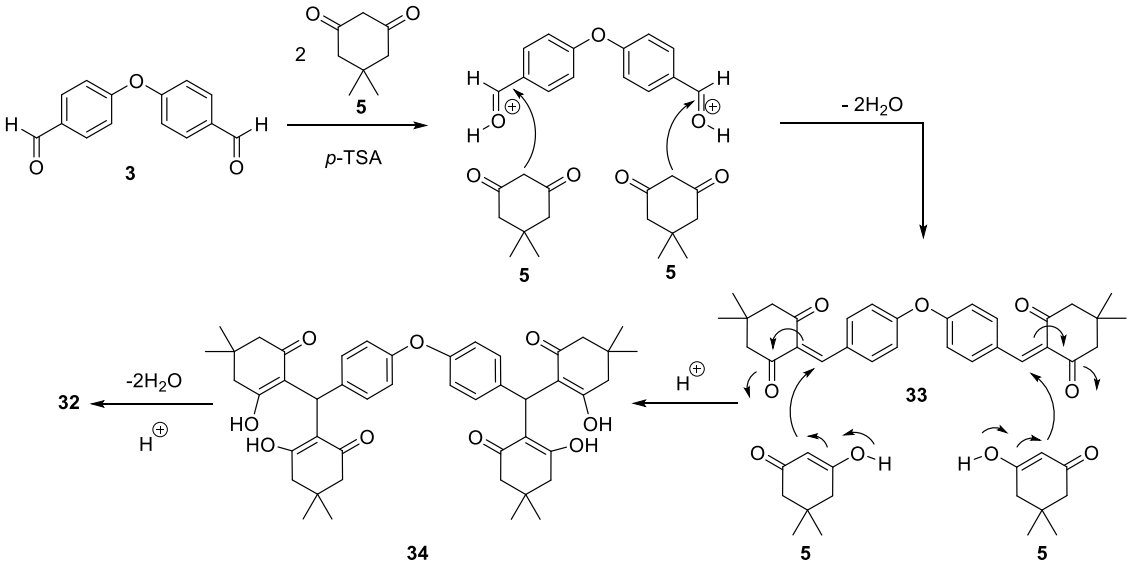
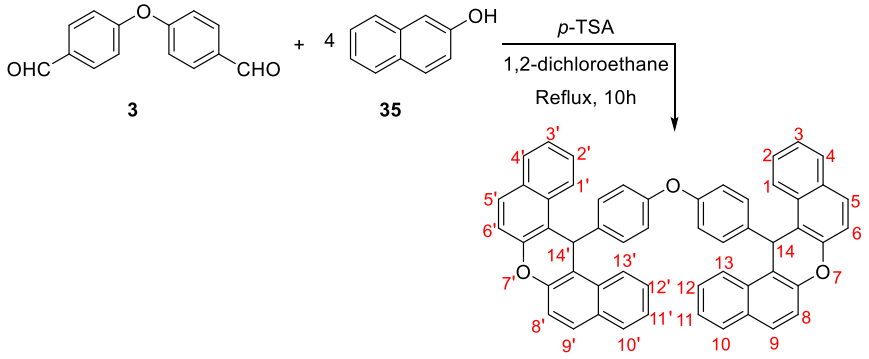
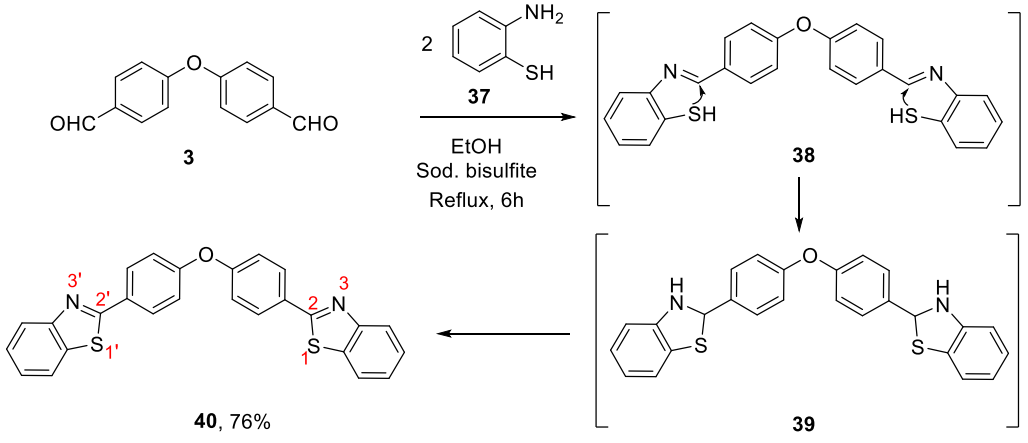
Scheme 11. Plausible Mechanism for the Formation of 32



Scheme 12. Synthesis of 14,14′-(Oxybis(4,1-phenylene))bis(14*H*-dibenzo[*a*,*j*]xanthene) 36



Scheme 13. Synthesis of 2,2′-(Oxybis(4,1-phenylene))bis(benzo[*d*]thiazole) 40



spectrum of **25** displayed signals is at 119.4 and 120.5 ppm characteristic for the CN groups, respectively. The IR spectrum of compound **25** displayed bands at 3420, 3362, and 3297 cm^{-1} characteristics for the NH_2 groups. In addition, the bands at 2218 cm^{-1} can be attributed to the CN groups.

Studying the reactivity of the 4,4′-oxydibenzaldehyde **3** was extended to include the synthesis of bis(hexahydro-1*H*-xanthene-1,8-dione) **32** through the reaction of one equivalent of 4,4′-oxydibenzaldehyde **3** with four equivalents of dimedone **5** in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an acidic catalyst (Scheme 10). Although a variety of methods have been described for the synthesis of xanthenes; nevertheless, the condensation of aldehydes with cyclic 1,3-dicarbonyl com-

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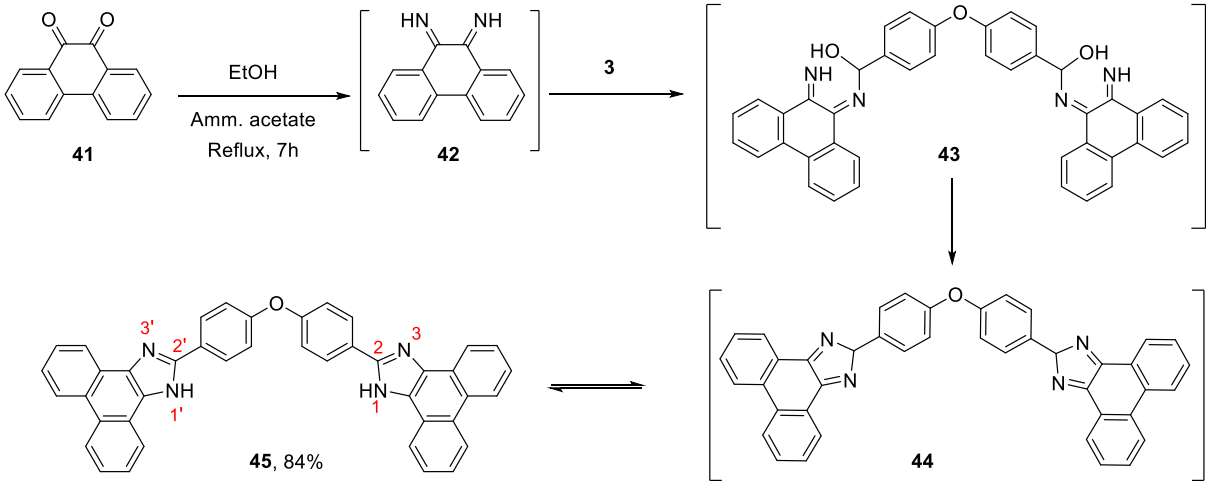
Scheme 14. Synthesis of 2,2′-(Oxybis(4,1-phenylene))bis(1*H*-phenanthro[9,10-*d*]imidazole) 45



pounds was discovered to be the most straightforward method for the synthesis of symmetric xanthenes.[65−67]

The constitution of compound **32** was verified based on ^{1}H NMR spectra that indicated the presence of two singlet signals at 0.91 and 1.05 ppm for the methyl groups in addition to a characteristic signal at 4.51 ppm for the xanthene-H9. Also, it indicated two multiplets at 2.07−2.28 and 2.53 for the xanthene-H2,4,5,7. All other signals appear at their expected positions. Besides, ^{13}C NMR indicated 13 signals corresponding to 13 different carbons. It displayed signals at 31.9 and 196.2 ppm characteristics for the C9′ and C═O groups, respectively. The IR spectrum of compound **32** displayed bands at 1690 cm^{-1} characteristic of the C═O group.

Scheme 11 illustrates the possible process by which the interaction of dimedone with corresponding aldehyde **3** results in the production of **32**. Knoevenagel condensation of 4,4′-oxydibenzaldehyde **3** with 2 mol of dimedone **5** in the presence of *p*-TSA affords bis(methaneylylidene)bis(5,5-dimethylcyclohexane-1,3-dione) **33**. Michael's addition reaction of **32** toward dimedone **5** results in the formation of the Michael adduct **34**, which loses two molecules of water to give the final isolable product **32**.

Likewise, the 4,4′-oxydibenzaldehyde **3** was utilized as a versatile precursor to the novel 14,14′-(oxybis(4,1-phenylene))-bis(14*H*-dibenzo[*a*,*j*]xanthene) **36** through its reaction with 2-naphthol **35** in the presence of *p*-TSA (Scheme 12).

Our study also included the cyclocondensation of 4,4′-oxydibenzaldehyde **3** with 2-aminothiophenol **37** in refluxing ethanol in the presence of $NaHSO_3$. The 2,2′-(oxybis(4,1-phenylene))bis(benzo[*d*]thiazole) **40** was produced in 76% yield (Scheme 9). The reaction begins with the condensation of **3** with **37** to afford Schiff's base intermediate **38**. The nucleophilic addition of SH to the imine bond in **38** affords **39** that readily oxidized in the presence of sodium bisulfite into **40** (Scheme 13).

Additionally, the cyclocondensation reaction of 4,4′-oxydibenzaldehyde **3** with phenanthrene-9,10-diimine **42** (generated in situ by the action of ammonium acetate on 9,10-phenanthrenequinone **41**) produced the corresponding 2,2′-(oxybis(4,1-phenylene))bis(1*H*-phenanthro[9,10-*d*]imidazole) **45** via the intermediacy of **43** and **44**. Compound **45** can be considered a new component for blue light-emitting materials (Scheme 14).[68]

CONCLUSIONS

We developed a fast and effective method for producing a variety of bis-thiazoles, bis-fused dihydropyrans, and other bis-heterocycles using 4,4′-oxydibenzaldehyde as a precursor. This adaptable precursor was subsequently employed to create high yields of the target compounds in the three-component Michael and other cyclocondensation processes. This technique offers gentle reaction conditions, is easy to use, has a large structural variety, and has a strong functional group tolerance. We believe that combining adaptable structural motifs in heterocyclic systems with a diphenyl ether core, which is commonly employed in medicines, will improve the biological activities of the resultant heterocyclic systems.

EXPERIMENTAL SECTION

General. Melting points were measured with a Stuart melting point apparatus and were uncorrected. The IR spectra were recorded using a FTIR Bruker-vector 22 spectrophotometer as KBr pellets. The ^{1}H NMR spectra were recorded in DMSO-d_6 as a solvent on a Varian Gemini NMR spectrometer at 300 MHz using TMS as the internal standard. Chemical shifts were reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS-QP-1000 EX mass spectrometer in an EI (70 eV) model. The elemental analyses were performed at the Microanalytical Center at Cairo University.

*4,4′-(Oxybis(4,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile) (**6**). Method A.* A mixture of bisaldehyde **3** (1 mmol) and malononitrile **4** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 30 min. Dimedone **5** (2 mmol) in 10 mL of ethanol was then added, and the reaction mixture was further heated at reflux for 3 h. The isolated precipitate was filtered, dried, and recrystallized from ethanol/dioxane (5/1) to give **6** as pale yellow crystals.

Method B. A mixture of dimalononitrile **7** (1 mmol) and dimedone **5** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 3 h. The isolated precipitate was filtered, dried, and recrystallized from ethanol/dioxane (5/1) to give pure compound **6** as pale yellow crystals.

% Yields (Method A 73%, Method B 74%); mp: 250−252 °C; IR (KBr): ν = 3394, 3330 (NH_2), 2190 (CN), 1676 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.96 (s, 6H, $2CH_3$), 1.03 (s, 6H, $2CH_3$), 2.10−2.27 (m, 4H, $2CH_2$), 2.49−2.51 (m, 4H,

https://doi.org/10.1021/acsomega.3c09081
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2CH_2), 4.17 (s, 2H, 2CH), 6.90 (d, J = 8.8 Hz, 4H, Ar−H), 6.96 (br, 4H, 2NH_2), 7.13(d, J = 8.8 Hz, 4H, Ar−H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.9, 28.3, 31.8, 34.9, 43.8, 50.0, 58.2, 112.7, 118.4, 119.8, 128.7, 139.8, 155.2, 158.5, 162.5, 195.8. MS (EI, 70 eV) m/z: 602 [M]$^+$. Anal. For $C_{36}H_{34}N_4O_5$ calcd: C, 71.74; H, 5.69; N, 9.30. Found: C, 71.58; H, 5.51; N, 9.16%.

*2,2′-((Oxybis(4,1-phenylene))bis(methaneylylidene))-dimalononitrile (**7**).* A mixture of bisaldehyde **3** (1 mmol), malononitrile **4** (2 mmol), and 2 drops of triethyl amine was heated at reflux for 2 h. The isolated yellow precipitate was filtered, dried, and recrystallized from ethanol/water (5/1) to give **7** as pale yellow crystals. Yield (65%); mp: 178−180 °C; IR (KBr): ν = 2192 (CN) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.36 (d, J = 8.8 Hz, 4H, Ar−H), 8.06 (d, J = 8.8 Hz, 4H, Ar−H), 8.52 (s, 2H, vinyl-H). MS (EI, 70 eV) m/z: 322 [M]$^+$. Anal. For $C_{20}H_{10}N_4O$ calcd: C, 74.53; H, 3.13; N, 17.38. Found: C, 74.67; H, 3.24; N, 17.48%.

*2,2′-((Oxybis(4,1-phenylene))bis(methaneylylidene))bis-(1H-indene-1,3(2H)-dione) (**11**). Method A.* A mixture of dimalononitrile **7** (1 mmol) and 1,3-indandione **8** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 30 min. The isolated precipitate was filtered, dried, and recrystallized from DMF to give pure compound **11** as yellow crystals.

Method B. A mixture of bisaldehyde **3** (1 mmol) and 1,3-indandione **8** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 30 min. The isolated yellow precipitate was filtered, dried, and recrystallized from DMF to give pure compound **11** as yellow crystals.

% Yields (Method A 63%, Method B 65%); mp: 272−274 °C; IR (KBr): ν = 1692 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.27 (d, J = 8.9 Hz, 4H, Ar−H), 7.84 (s, 2H, 2═CH), 7.94−7.96 (m, 8H, Ar−H), 8.63 (d, J = 8.9 Hz, 4H, Ar−H). MS (EI, 70 eV) m/z: 482 [M]$^+$. Anal. For $C_{32}H_{18}O_5$ calcd: C, 79.66; H, 3.76. Found: C, 79.48; H, 3.57%.

*5,5′-((Oxybis(4,1-phenylene))bis(methaneylylidene))bis-(pyrimidine-2,4,6(1H,3H,5H)-trione) (**14**). Method A.* A mixture of dimalononitrile **7** (1 mmol) and barbituric acid **12** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 2 h. The isolated yellow precipitate was filtered, dried, and recrystallized from glacial acetic acid to give **14** as pale yellow crystals.

Method B. A mixture of bisaldehyde **3** (1 mmol) and barbituric acid **12** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 2 h. The isolated yellow precipitate was filtered, dried, and recrystallized from glacial acetic acid to give **14** as pale yellow crystals.

% Yields (Method A, 84%, Method B, 85%); mp: >300 °C; IR (KBr): ν = 3438 (NH), 1672 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.9 (d, J = 8.7 Hz, 4H, Ar−H), 8.28 (s, 2H, 2═CH), 8.30 (d, J = 8.7 Hz, 4H, Ar−H), 9.98 (s, 2H, 2═CH), 11.22 (s, 2H, 2NH), 11.35 (s, 2H, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 118.4, 128.5, 132.2, 136.8, 150.3, 153.9, 159.0, 162.0, 163.7. MS (EI, 70 eV) m/z: 446 [M]$^+$. Anal. For $C_{22}H_{14}N_4O_7$ calcd: C, 59.20; H, 3.16; N, 12.55. Found: C, 59.07; H, 3.03; N, 12.38%.

*4,4′-(Oxybis(4,1-phenylene))bis(2-amino-7,7-dimethyl-5-oxo-1-(p-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile) (**16**).* A mixture of bisaldehyde **3** (1 mmol), malononitrile **4** (2 mmol), and 5,5-dimethyl-3-(*p*-tolylamino)cyclohex-2-en-1-one **15** (2 mmol) in ethanol (10 mL) in the presence of 2 drops of piperidine was heated at reflux for 3 h. The so-formed crude product was collected by filtration, allowed to dry, and further purified by crystallization from dioxane to give compound **16** as green crystals. Yield (61%); mp: >300 °C; IR (KBr): ν = 3441, 3328 (NH_2), 2185 (CN), 1685 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.74 (s, 6H, 2CH_3), 0.88 (s, 6H, 2CH_3), 1.99−2.21 (m, 8H, 2CH_2), 2.39 (s,6H, 2CH_3), 4.46 (s, 2H, 2CH), 5.25 (br s, 4H, 2NH_2), 7.27−7.39 (m, 16H, Ar−H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.9, 26.4, 29.1, 32.0, 35.8, 41.0, 43.8, 49.3, 60.1, 111.7, 118.5, 121.7, 128.4, 129.7, 130.8, 133.5, 139.4, 150.4, 151.3, 155.2, 195.0. MS (EI, 70 eV) m/z: 780 [M]$^+$. Anal. For $C_{50}H_{48}N_6O_3$ calcd: C, 76.90; H, 6.20; N, 10.76. Found: C, 76.73; H, 6.07; N, 10.59%.

*Diethyl 7,7′-(oxybis(4,1-phenylene))bis(6-cyano-3,10,10-trimethyl-4,8-dioxo-5,7,8,9,10,11-hexahydro-4H-thieno-[3′,2′:5,6]pyrimido[1,2-a]quinoline-2-carboxylate) (**20**).* A mixture of bisaldehyde **3** (1 mmol), malononitrile **4** (2 mmol), and diethyl 5-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino)-3-methylthiophene-2,4-dicarboxylate **18** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 6 h. The isolated precipitate was filtered, dried, and recrystallized from ethanol/dioxane (5/1) to give compound **20** as yellow crystals. Yield (68%); mp: 240−242 °C; IR (KBr): ν = 3433 (NH), 2198 (CN), 1715 (CO ester), 1662 (CO amide) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.94 (s, 6H, 2CH_3), 1.13 (s, 6H, 2CH_3), 1.28 (t, J = 7.2 Hz, 6H, 2COOCH_2CH_3), 2.11−2.16 (m, 4H, 2COOCH_2CH_3), 2.53−2.59 (m, 4H, 2CH_2), 2.64 (s, 6H, 2CH_3), 4.30 (q, J = 7.2 Hz, 4H, CH_2), 4.60 (s, 2H, CH), 6.86 (d, J = 8.1 Hz, 4H, Ar−H), 7.15 (d, J = 8.1 Hz, 4H, Ar−H), 11.55 (br, 2H, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.2, 14.3, 24.8, 30.1, 35.2, 36.0, 40.3, 49.5, 61.3, 71.3, 117.3, 118.5, 118.8, 119.0 (2 Ar−C), 119.7, 128.5, 137.0, 144.2, 145.3, 148.1, 149.5, 155.8, 156.9, 161.4, 195.5. MS (EI, 70 eV) m/z: 988 [M]$^+$. Anal. For $C_{54}H_{48}N_6O_9S_2$ calcd: C, 65.57; H, 4.89; N, 8.50. Found: C, 65.39; H, 4.72; N, 8.36%.

*5,5′-(Oxybis(4,1-phenylene))bis(2,7-diaminopyrazolo[1,5-a]pyridine-3,4,6-tricarbonitrile) (**25**).* A mixture of bisaldehyde **3** (1 mmol), malononitrile **4** (2 mmol), and 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **22** (2 mmol) in ethanol (10 mL) containing 2 drops of piperidine was heated at reflux for 6 h. The isolated precipitate was filtered, dried, and recrystallized from DMF to give compound **25** as brown crystals. Yield (66%); mp: >300 °C; IR (KBr): ν = 3420, 3362, 3297 (NH_2), 2218 (CN) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.71 (s, 4H, 2NH_2), 7.29 (d, J = 8.7 Hz, 4H, Ar−H), 7.65 (d, J = 8.7 Hz, 4H, Ar−H), 8.68 (br, 4H, 2NH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 71.7, 79.3, 84.4, 113.2, 114.8, 115.7, 119.4, 120.5, 130.3, 131.8, 142.6, 148.1, 158.0, 161.3. MS (EI, 70 eV) m/z: 612 [M]$^+$. Anal. For $C_{32}H_{16}N_{14}O$ calcd: C, 62.74; H, 2.63; N, 32.01. Found: C, 62.57; H, 2.42; N, 31.86%.

*9,9′-(Oxybis(4,1-phenylene))bis(3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione) (**32**).* A mixture of bisaldehyde **3** (1 mmol) and dimedone **5** (4 mmol) in ethanol (10 mL) containing a catalytic amount of *p*-TSA was heated at reflux for 6 h. The reaction mixture was then allowed to cool to room temperature. The collected product was filtered, dried, and recrystallized from ethanol to give **32** as pale yellow crystals. Yield (74%); mp: 268−270 °C; IR (KBr): ν = 1690 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.91 (s, 12H, 4CH_3), 1.05 (s, 12H, 4CH_3), 2.07−2.28 (m, 8H, 4CH_2), 2.53 (m, 8H, 4CH_2), 4.51 (s, 2H, 2CH), 6.77 (dd, J = 8.7, 1.5 Hz, 4H, Ar−H), 7.13 (dd, J = 8.7, 1.5 Hz, 4H, Ar−H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.5, 28.6, 30.5, 31.9, 40.3, 50.0, 114.3, 117.9, 129.4, 139.3, 154.8, 163.0, 196.2. MS (EI, 70 eV) m/z:

https://doi.org/10.1021/acsomega.3c09081
ACS Omega 2024, 9, 4073−4084

714 $[M]^+$. Anal. For $C_{46}H_{50}O_7$ calcd: C, 77.28; H, 7.05. Found: C, 77.11; H, 6.84%.

*14,14′-(Oxybis(4,1-phenylene))bis(14H-dibenzo[a,j]-xanthene) (**36**).* A mixture of bisaldehyde **3** (1 mmol) and 2-naphthol **35** (4 mmol) in 1,2-dichloroethane (10 mL) containing a catalytic amount of *p*-TSA was heated at reflux for 10 h. The isolated precipitate was filtered, dried, and recrystallized from dioxane to give **36** as pink crystals. Yield (63%); mp: 290−292 °C; IR (KBr): ν = 3054, 2920 (aliphatic and aromatic CH), 1589 (C═C stretch) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.89 (s, 2H, 2CH), 6.52 (d, J = 8.7 Hz, 4H, Ar−H), 7.37−7.61 (m, 16H, Ar−H), 7.87 (dd, J = 8.5, 4.4 Hz, 8H, Ar−H), 8.57 (d, J = 8.7 Hz, 4H, Ar−H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 35.8, 117.4, 117.7, 118.2, 123.3, 124.5, 127.0, 128.6, 129.0, 129.3, 130.6, 130.8, 140.4, 148.0, 154.4. MS (EI, 70 eV) m/z: 730 $[M]^+$. Anal. For $C_{54}H_{34}O_3$ calcd: C, 88.74; H, 4.69. Found: C, 88.59; H, 4.56%.

*2,2′-(Oxybis(4,1-phenylene))bis(benzo[d]thiazole) (**40**).* A mixture of bisaldehyde **3** (1 mmol) and 2-aminothiophenol **37** (2 mmol) in absolute ethanol (10 mL) containing a catalytic amount of $NaHSO_3$ was heated at reflux for 6 h. The reaction mixture is then poured into water. The isolated precipitate was filtered, dried, and recrystallized from glacial acetic acid to give pure compound **40** as pale yellow crystals. Yield (76%); mp: >300 °C; IR (KBr): ν = 3058 (CH), 1591 (C═C stretch) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 6.47−7.01 (m, 2H, Ar−H), 7.14 (d, J = 8.7 Hz, 2H, Ar−H), 7.30 (d, J = 8.7 Hz, 2H, Ar−H), 7.44−7.58 (m, 4H, Ar−H), 8.02−8.19 (m, 6H, Ar−H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 119.1, 120.3, 123.3, 126.1, 127.3, 128.8, 129.9, 136.4, 153.5, 154.2, 165.9. MS (EI, 70 eV) m/z: 436 $[M]^+$. Anal. For $C_{26}H_{16}N_2OS_2$ calcd: C, 71.54; H, 3.69; N, 6.42. Found: C, 71.33; H, 3.48; N, 6.27%.

*2,2′-(Oxybis(4,1-phenylene))bis(1H-phenanthro[9,10-d]-imidazole) (**45**).* A mixture of bisaldehyde **3** (1 mmol) and phenanthrene-9,10-diimine **41** (2 mmol) in absolute ethanol (10 mL) containing ammonium acetate (5 mmol) was heated at reflux for 7 h. The so-formed crude product was collected by filtration, allowed to dry, and recrystallized from dioxane to give **45** as brown crystals. Yield (84%); mp: 210−212 °C; IR (KBr): ν = 3429 (NH), 2919 (CH), 1600 (C═C stretch) cm^{-1}. ^1H NMR (300 MHz, DMSO) δ: 7.37 (d, J = 8.9 Hz, 4H, Ar−H), 7.59−7.80 (m, 8H, Ar−H), 8.40 (d, J = 8.9 Hz, 4H, Ar−H), 8.58 (dd, J = 16.9, 7.7 Hz, 4H, Ar−H), 8.86 (t, J = 9.2 Hz, 4H, Ar−H), 13.44 (s, 2H, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 118.0, 118.8, 119.2, 119.9, 122.0, 122.4, 118.1, 119.3, 122.0, 124.0, 125.3, 126.1, 127.2, 127.6, 128.3 (2 Ar−C), 148.8, 157.3. MS (EI, 70 eV) m/z: 602 $[M]^+$. Anal. For $C_{42}H_{26}N_4O$ calcd: C, 83.70; H, 4.35; N, 9.30. Found: C, 83.51; H, 4.21; N, 9.18%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c09081.

^1H NMR spectrum of compound **6**; ^{13}C NMR spectrum of compound **6**; ^1H NMR spectrum of compound **7**; ^1H NMR spectrum of compound **11**; ^1H NMR spectrum of compound **14**; ^{13}C NMR spectrum of compound **14**; ^1H NMR spectrum of compound **16**; ^{13}C NMR spectrum of compound 16; ^1H NMR spectrum of compound **20**; ^{13}C NMR spectrum of compound **20**; ^1H NMR spectrum of compound **25**; ^{13}C NMR spectrum of compound **25**; ^1H NMR spectrum of compound **32**; ^{13}C NMR spectrum of compound **32**; ^1H NMR spectrum of compound **36**; ^{13}C NMR spectrum of compound **36**; ^1H NMR spectrum of compound **40**; ^{13}C NMR spectrum of compound 40; ^1H NMR spectrum of compound **45**; and ^{13}C NMR spectrum of compound **45** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported and funded by the Deanship of Scientific Research at Imam Mohammad Ibn Saud Islamic University (IMSIU) (grant no. IMSIU-RG23128).

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