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4-(*N*-Phthalimido)phenyl Isonitrile as a Novel Convertible Isocyanide Analogue with the Odorless Property as an Extra Bonus

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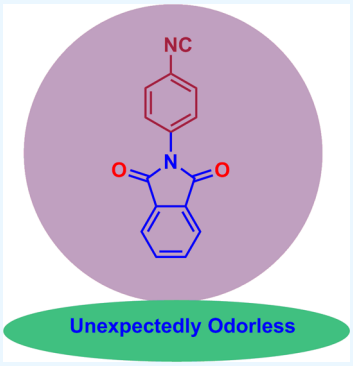
ABSTRACT: We explored a new isonitrile, namely 4-(*N*-phthalimido)phenyl isonitrile, with extraordinary features. The novel isocyanide has a pharmacophore, the phthalimido (Pht) group, that possesses promising pharmaceutical activities. We found that the novel isonitrile is unexpectedly odorless as an extra bonus which makes its handling easy in organic synthesis to serve as a scaffold for building several new amide derivatives through multicomponent reactions, overcoming the stink of common aromatic isonitriles such as phenyl isonitrile, benzyl isonitrile, *p*-nitrophenyl isonitrile, and ethyl 4-isocyano benzoate. The novel isonitrile **9** serves as a source of *N*-protected isonitrile with a Pht group, where the Pht group can be easily removed via hydrazinolysis, affording the corresponding primary amine/alcohol scaffold which could be used as a precursor to synthesize Passerini products via acylation directly to afford Passerini adducts **14** and **15** without carrying out the traditional Passerini three-component reaction; this new isonitrile is considered as a novel convertible isocyanide analogue.



1. INTRODUCTION

Since the first discovery of isocyanides by Lieke[1] in 1859, it is clear that these compounds have great potential applications for organic synthesis such as Ugi[2,3] and Passerini[4,5] multicomponent reactions (MCRs). The isocyanide group shows intermediate behavior between carbene and triple bond character, with a high degree of reactivity. Despite the undeniable role of isonitriles in organic synthesis and atom economy in many recorded MCRs, such as the Passerini three-component reaction (P-3CR)[4,6] and Ugi four-component reaction (U-4CR),[7,8] for the synthesis of pharmaceuticals, natural products, and perplexing organic compounds,[3,5] the overpowering stink of isonitriles severely limits their use, and one can say that in the realm of stinkers isonitriles may have no contender. Therefore, most researchers around the world have banned the use of isonitriles in their laboratories.

It is worth noting that there have been several previously reported attempts to bypass the horrific odor of isocyanides, including Wang's method via the in situ preparation of isocyanides[9] within the same reaction vessel prior to attempting the main target reaction. Furthermore, a Russian research group[10] recently reported a smart way to reduce the horrible odor of isocyanides along with preserving their valuable chemical properties by forming an adduct with iodoperfluorobenzenes via a halogen bond between isocyanides and the iodine of iodoperfluorobenzenes, but this produced a lot of impurities in the resultant MCR products. The novelty of this work comes from the synthesis of a novel isonitrile containing a phthalimido group (Pht) with plenty of desirable properties such as the presence of a protecting group, a pharmacophore moiety, and odorlessness as an extra bonus. Moreover, Pht-based compounds demonstrate therapeutic and pharmaceutical applications and thus function as leading points for the design of novel drug candidates, showing safe and effective anticancer[11−13] and antimicrobial[14] activities. Moreover, the Pht group participates in a vast number of potent anticancer drugs, such as thalidomide[11] **1**, pomalidomide[12] **2**, and lenalidomide[13] **3**, and a strong anticonvulsant and antiepileptic drug, taltrimide[15] **4** (Figure 1).

Alternatively, the synthetic value of the Pht group cannot be neglected, thus the efficacy exhibited by the Pht moiety makes it a valuable synthon, providing a source of a masked primary amine group, which can be recovered directly by hydrazinolysis of the adduct via Gabriel synthesis[16] using Ing−Manske's procedure to afford a new amine which can be used as a precursor for the synthesis of Passerini adducts without using any isonitrile via direct acylation. Within this context, it pushes our interest to prepare a new isonitrile containing a Pht group as the pharmacophoric moiety, which unexpectedly exhibited odorless properties as an extra bonus.

2. RESULTS AND DISCUSSION

Herein, our endeavor is to prepare a new isocyanide containing a Pht group, which may give a promising biologically active isonitrile, namely, 4-(*N*-phthalimido)phenylisonitrile (**9**). The

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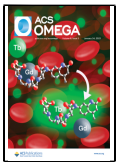

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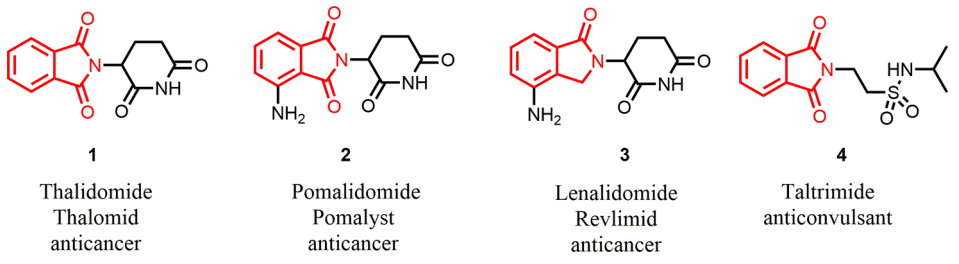
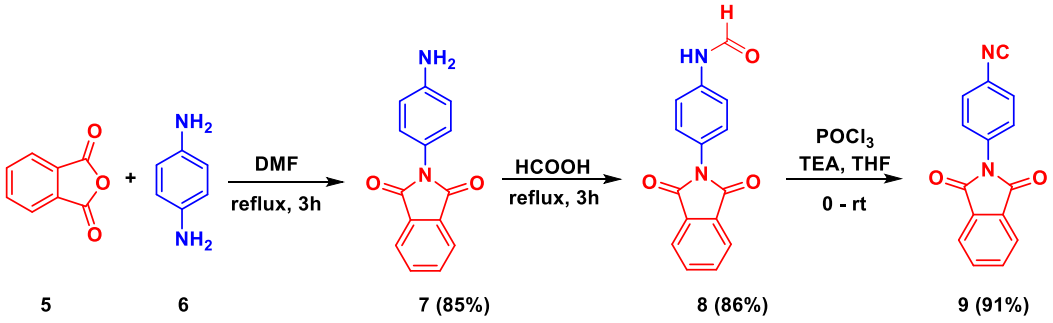


Figure 1. Structures of drugs containing the Pht group.

Scheme 1. Synthesis of 4-(*N*-Phthalimido)phenyl Isonitrile (9)



remarkable features of **9** are its excellent stability and ease of preparation, with a good overall yield of 66.5% and a low-cost synthetic route; in addition, it is not intimidating that it is odorless and allows easy handling during organic synthesis. Scheme 1, demonstrates the synthesis of 4-(*N*-phthalimido)-phenyl isonitrile (**9**), which was accomplished by several synthetic protocols, such as Ugi, Hofmann, and Wang methods, to achieve the optimized reaction conditions.

Compound **9** was prepared from *p*-phenylenediamine (**6**) by the traditional insertion reaction with phthalic anhydride (**5**) via reflux in DMF for 3 h, affording the corresponding aniline derivative 2-(4-aminophenyl)isoindoline-1,3-dione (**7**) efficiently, followed by a formylation step utilizing formic acid to give the formamide derivative **8**. The final step was dehydration of formamide **8** accomplished by Ugi's method using $POCl_3$/triethylamine (TEA)[7] in different solvents; the ideal solvent was found to be tetrahydrofuran (THF) which gave **9** with a yield over than 90%, superior to chloroform, DCM, and a mixture (1:1) of both. On the other hand, the dehydration step using Wang's method utilizing Ph_3P/I_2/TEA[17] in $CHCl_3$ gave **9** with a poor yield. Also, isocyanide **9** was not obtained using Hofmann's method by reaction of **7** with $CHCl_3$/KOH[18] (Table 1).

The structures of all the synthesized compounds **7**–**9** were confirmed by spectroscopic analysis. The IR spectra of **7**, Figure S3, shows a split band at 3462 and 3368 cm^{-1} corresponding to NH_2; the ^1H NMR spectra of **7**, Figure S1, shows a singlet signal at δ_H = 5.32 ppm corresponding to NH_2 and an aromatic proton resonating from δ_H = 7.88 to 6.59 ppm; in addition, the ^{13}C NMR spectra of **7**, Figure S2, shows a strong signal at δ_C = 167.7 ppm corresponding to the C═O moiety of the Pht group. While the ^1H NMR spectra of formamide **8**, Figure S4, shows two characteristic signals at δ_H = 10.37 and 8.28 ppm corresponding to H−C═O and N−H of the *N*-formamide group, respectively; the ^1H NMR spectra of **8**, Figure S4, shows the presence of tautomerization of the formamide group in the ratio ≈ 74:26% for amido/iminol, respectively. Also, the ^{13}C NMR spectra of **8** and the IR spectra confirm the tautomerization of the formamide group, Figures S5 and S6, respectively. The structure of **9** was confirmed by the IR spectra, Figure S9, that shows sharp intense bands at 2121 cm^{-1} attributed to the NC group and at 1747 cm^{-1} attributed to C═O cm^{-1}, whereas the ^1H NMR spectra, Figure S7, shows aromatic protons resonating from δ_H = 7.95 to 7.57 ppm. The ^{13}C NMR spectra, Figure S8, shows two characteristic signals at δ_C = 167.7 and 160.4 ppm corresponding to the C═O and NC carbons, respectively, where the isocyano group resonates between double and triple bonds. In addition to the exact molecular mass of **9** reported by electron ionization mass spectrometry (EI-MS), a molecular ion peak was observed at *m*/*z* 248.77, Figure S10.

Furthermore, the experimental UV/vis electronic spectra of **9** were obtained in DCM, which clearly show two major broad spectral bands at 248 and 233 nm. Thus, the reported bands were assigned to HOMO → LUMO via $\pi-\pi^*$ excitation (Figure 2).

Moreover, the Passerini reaction[4] using the new isonitrile **9** was carried out using excess cyclohexanone[6] and *o*-nitrobenzoic acid, affording the corresponding Passerini product *α*-acyloxy carboxamide **12**, Scheme 2. The structure of **12** was confirmed by the ^1H NMR spectrum, Figure S11, where N−H amide appears as a singlet at δ_H = 9.84 ppm; the ^{13}C NMR spectrum, Figure S12, shows three characteristic peaks for C═O groups of esters, phthalimido, and amide at δ_C = 170.6,

Table 1. Optimization of the Reaction Conditions of Synthesis of Isonitrile 9

method	reagents	solvent	yield
Ugi	$POCl_3$/TEA 0 °C	CH_2Cl_2	>5%
		$CH_2Cl_2/CHCl_3$ 50:50	15%
		$CHCl_3$	22%
		THF	91%
Wang	Ph_3P/I_2/TEA 0 °C	$CHCl_3$	19%
Hofmann	KOH + $CHCl_3$ rt	$CHCl_3$	ND

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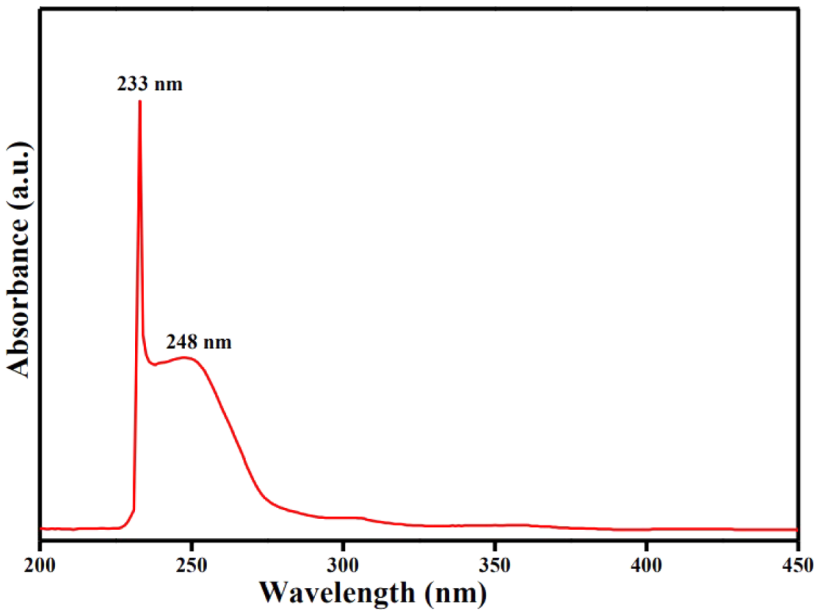
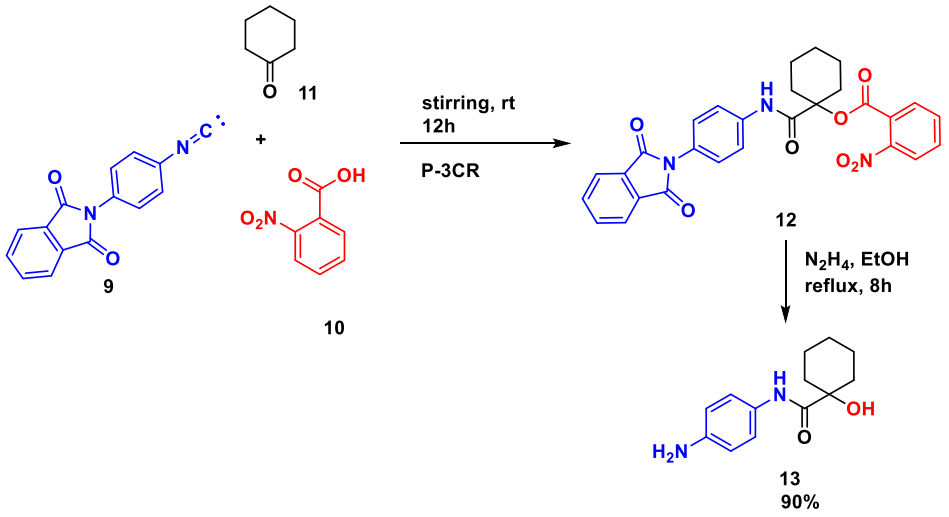


Figure 2. Experimental UV/vis spectra of **9**.

Scheme 2. Deprotection of the Pht Group from the Passerini Product



167.7, and 163.8 ppm; the IR spectrum, Figure S13, shows absorption bands at 3392 cm^{-1} for NH amide and at 1738 and 1708 cm^{-1} for CO. Deprotection of the Pht group of α-acyloxy carboxamide **12** via hydrazinolysis gave **13** that possessed the expected free primary aromatic amine group and the tertiary alcohol. The hydrolysis product opens a new horizon to novel and short synthetic pathways to prepare a library of an infinite number of Passerini products without conducting the Passerini reaction at all via acylation, protection, or peptide coupling tools. The structure of **13** was confirmed by the ^{1}H NMR spectra, Figure S14, where the signals for NH (amide), OH, and NH_2 protons appear at δ_H = 9.10, 5.31, and 4.94 ppm, respectively, and its ^{13}C NMR spectra, Figure S15, shows signals at δ_C = 175.4 and 74.3 ppm corresponding to C═O of amide and carbon tertiary alcohol, respectively. Also, the IR spectra of **13** shows split bands at 3364 and 3324 cm^{-1} corresponding to the NH_2 group overlapping with the br band of OH, Figure S16.

The importance of this novel isonitrile opens the door to preparing different uncommon Passerini products without using their corresponding isonitrile; for instance, coupling of **13** with benzene sulfonyl chloride or acetic anhydride at rt for 24 h in the presence of TEA as a solvent, Scheme 3, affords Passerini adducts **14** and **15**, respectively. The ^{1}H NMR spectra of **14**, Figure S17, shows characteristic peaks at δ_H = 9.86 and 5.50 ppm for O═C−NH and SO_2N−H, respectively; also, the ^{13}C NMR spectra, Figure S18, shows a distinctive signal at δ_C = 177.0 ppm corresponding to C═O of amide. Furthermore, the ^{1}H NMR spectra of **15**, Figure S19, shows two distinct peaks at δ_H = 9.84 and 9.41 ppm for O═C−NH (two amide groups); also, the ^{13}C NMR spectra, Figure S20, shows three characteristic signals at δ_C = 171.3, 169.9, and 168.5 ppm attributed to the C═O group of ester and two amide derivatives, respectively.

Furthermore, in order to prepare **14** and **15** via direct P-3CR, two uncommon isonitriles **16** and **18** were needed respectively. As illustrated in the retrosynthetic strategy,

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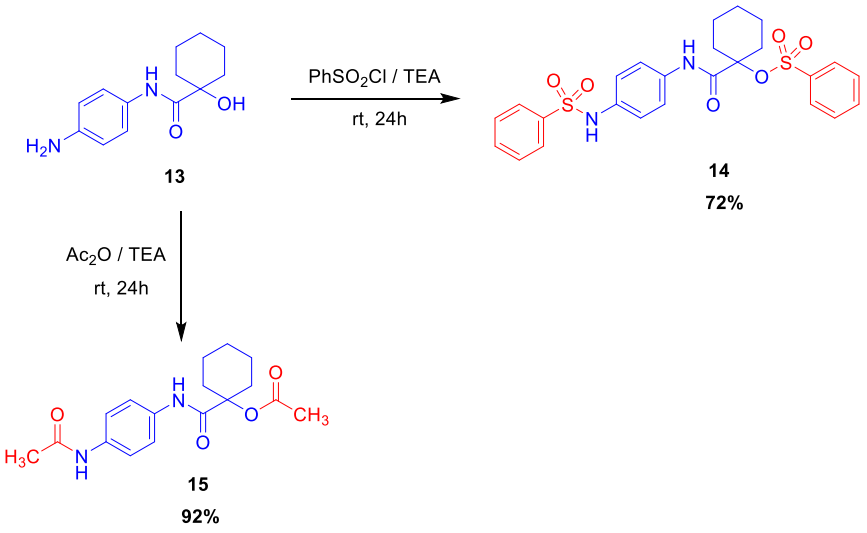
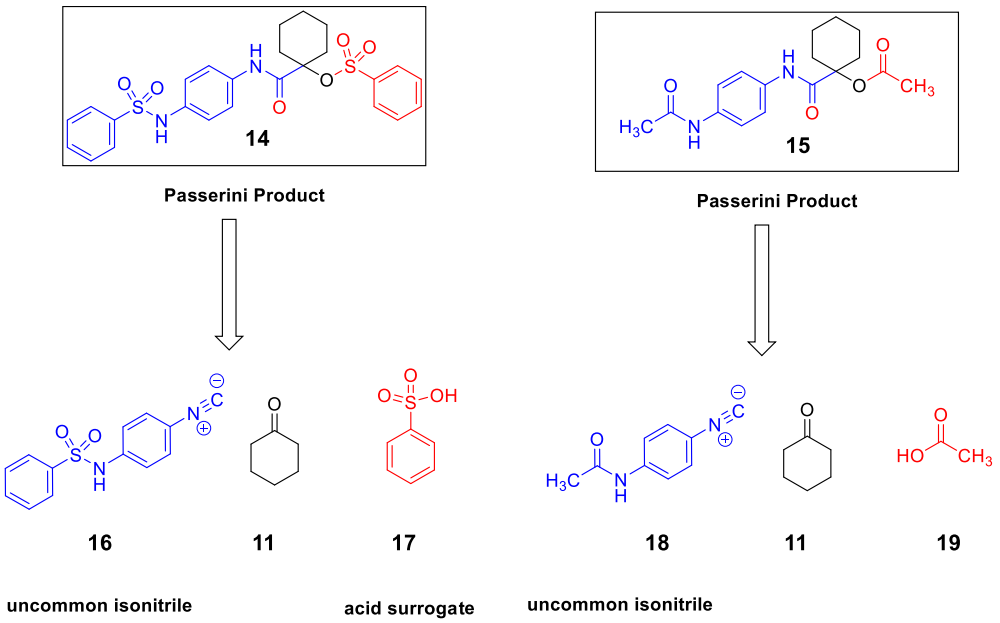
Scheme 3. Synthesis of α-Acyloxy Carboxamides without Isonitrile (without Isocyanide-Based MCR)



Scheme 4. Retrosynthetic Analysis of 14 and 15



Scheme 4, adduct **14** also requires the use of benzenesulfonic acid **17** in the Passerini reaction as carboxylic acid surrogate or **19**, which is not a common attempt, so we can say that the key compound **13** facilitates the synthetic protocol to obtain unusual Passerini products.

3. CONCLUSIONS

In the current study, we discovered a new isonitrile, namely 4-(*N*-phthalimido)phenyl isonitrile (**9**), that possesses a Pht group, which may have potential pharmaceutical applications. Moreover, the novel isonitrile is unexpectedly odorless as an extra bonus. The new isonitrile also serves as a convertible isonitrile analogue wherein the Pht group can be removed smoothly from the Passerini adduct via hydrazinolysis to afford the corresponding primary amine **13**. The key compound **13** can be used as a precursor to synthesize uncommon Passerini products via direct acylation without using isonitrile, which opens new horizons in MCRs.

4. EXPERIMENTAL SECTION

Details of used materials, equipment, and experimental procedures are presented in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06884.

Copy of ^{1}H NMR, ^{13}C NMR, IR, and EI-MS spectra of the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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