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Facile One-Pot Synthesis of 2-Aryl-substituted Nitriles and 2-Aryl-3-keto Nitriles via Benzyne Reaction

Sukanta Kamila, Benjamin Koh, and Edward R. Biehl
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Abstract: 2-Aryl-substituted nitriles were prepared in good to excellent yields in a one-pot reaction by the reaction of benzyne, generated using neutral conditions from (phenyl)[*o*-(trimethylsilyl)-phenyl]iodonium triflate, and 2-lithionitriles. 3-Keto nitriles substituted at the 2-position were obtained in good yields when these reactions were trapped with acid chlorides. The mechanism of the benzyne reaction in terms of a N-lithiobenzocyclobutanimine intermediate is discussed.

Keywords: benzyne, nucleophilic addition, Dials-Alder reaction, (phenyl)[o-trimethylsilyl)-phenyl]iodonium triflate, 2-aryl substituted nitriles

INTRODUCTION

During our studies on the use of nitrilases as biocatalysts in the room-temperature hydrolysis of nitriles to carboxylic acids, we needed several 2-arylalkanedinitriles, 2-aryl-3-ketotonitriles, and 3-aryl-2-hydroxyalkanenitriles. As shown in Fig. 1, 2-aryl-substituted nitriles are very important building blocks for synthesizing pyridine, carboxylic acids, primary amines, bicyclic amidines, lactones, aldehydes, and esters.[1] These nitriles are also valuable for constructing biologically active compounds verapamil (**1**)[2] and 3-alkylated-3-(4-aminophenyl) piperidine-2,6-diones (**2**).[3]

Compound **1** acts as a slow-acting calcium channel antagonist, and compound **2** has shown promise in many trials with postmenopausal and ovariectomized premenopausal women.[4–8]

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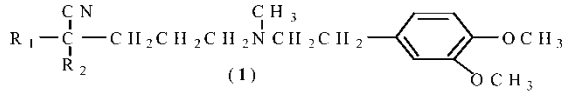
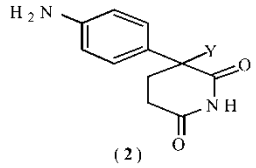


(1)

$R_1 = 3,4\text{-}(CH_3O)_2C_6H_3$ $R_2 = CH(CH_3)_2$ VERAPAMIL

$R_1 = 3,4\text{-}Cl_2C_6H_3$ $R_2 = CH(CH_3)_2$ DICHLOROVERAPAMIL

$R_1 = 3,4,5\text{-}(CH_3O)_3C_6H_2$ $R_2 = CH(CH_3)_2$ GALLOPAMIL



(2)

Y = H, Alkyl group

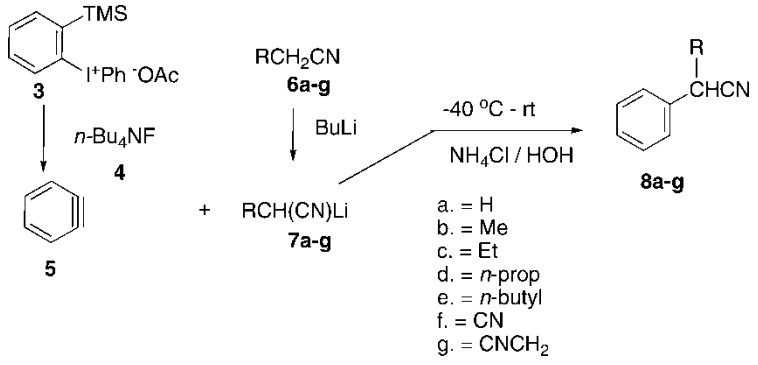
Figure 1. Typical biologically active compounds prepared from 2-aryl nitriles.

The classical way of preparing 2-aryl-substituted nitriles involves the displacement of an activated benzylic alcohol or halide with potassium cyanide at elevated temperatures, followed by 2-alkylation.[3,9] The benzyne reaction, however, provides 2-arylalkanenitriles in a more efficient one-pot reaction under less drastic conditions.[10] Typically, a benzyne intermediate is generated by the reaction of a haloarene with a strong base such as sodium amide or lithium diisopropyl amide (LDA) at low temperatures in the presence of freshly prepared 2-lithiated alkanenitrile. This anion then adds to benzyne to give 2-arylalkanenitrile, after proton quench. Although the base-mediated benzyne reaction provides 2-arylalkanenitriles under very mild conditions, the nitrile yields are negatively impacted by several pesky side reactions. These include amination of benzyne by the basic amine; reductive debromination of the haloarene, especially in the case of bromo- and iodobenzenes;[11] and the formation of di- and triarylalkanenitriles.

Recently, we[12] synthesized a variety of fused heterocycles by generating benzynes from the efficient hypervalent iodine benzyne precursor, (phenyl) [*o*-trimethylsilyl)-phenyl]iodonium triflate (**3**),[13] with Bu_4NF (TBAF) in the presence of heterodienes. Because the aforementioned side reactions were absent, the fused heterocycles were obtained in excellent yields (>80%). We have now extended this TBAF-mediated reaction to the synthesis of titled compounds and report the results herein.

RESULTS AND DISCUSSION

As shown in Scheme 1, a super-dry THF solution of iodonium triflate (**3**) and 2-lithionitrile (**7**), prepared by the reaction of **6** and *n*-BuLi, was cooled to −40°C. TBAF (**4**) was then added dropwise, and the resulting solution was allowed to warm to room temperature, during which time benzyne (**5**) was



Scheme 1.

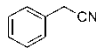
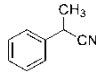
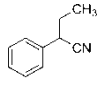
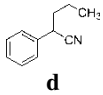
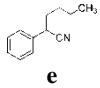
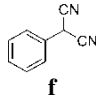
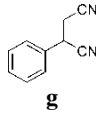
formed and subsequently trapped by **7a**–*g* to give the appropriate α-arylalkanenitrile **8a**–*g* after an ammonium chloride quench.

As shown in Table 1, the yields of **8a**–*e* ranged from essentially quantitative (entries 1–3) to good (entry 4, 85%) to modest (71% 5, 73%). The yields of dinitriles **8f, g** (entries 6 and 7) are modest (71% and 60%, respectively) but are actually quite good when compared to those prepared by the classical benzyne method, which gives mainly intractable tars. Further, other nonbenzyne procedures generally require longer reaction times, higher temperatures, and/or more stages. For example, the anaerobic, solid-supported Ru-catalyzed preparation of **8e** requires heating at 20 h at 180°C,[14] and the preparation of **8f** by the cross-coupling reaction of bromobenzene and malonitrile requires stirring at 15°C for 12 h[15] or at 85°C for 10 h.[16]

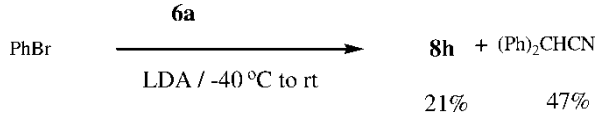
To see if 2-lithioarylacetonitriles might also react with **5** to give 2-arylated nitriles, we generated benzyne (**5**) from **3** and trapped it with 2-lithiophenylacetonitrile. However, as shown in Table 1 (entry 8), the rearranged 2-benzylbenzonitrile (**8 h**) was obtained in 71% yield. This was surprising in that we had previously found that arynes lacking electron-donating groups reacted with 2-lithioarylacetonitriles to give mainly unrearranged 2-arylacetonitriles.[17] However, we had not studied the reaction of benzyne itself with 2-lithiophenylacetonitrile. Thus, we repeated this reaction under classical benzyne conditions ($PhBr/PhCH_2CN/LDA$ in THF) and (as shown in Scheme 2) obtained a mixture **8 h** (21%) and 2,2-diphenylacetonitrile (47%). Thus, our benzyne method reported here should prove valuable for the synthesis of 2-benzylbenzonitriles, which are important precursors to 9-amino analogs arylnapthofuranone ligan derivatives.[18]

We next carried out the reaction of benzyne (**5**) with 2-lithionitriles **7a**–*h* and trapped the aryne–nitrile anion adduct with a variety of electrophilic trapping reagents, the results of which are shown in Table 2.

Table 1. α-Lithionitriles **8** by NH_4Cl quench of reaction **7** with **5**

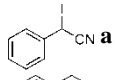
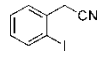
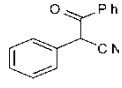
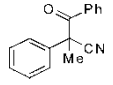
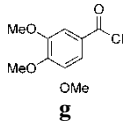
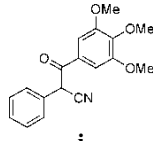
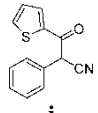
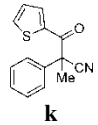
Entry	α-Lithionitrile **7**	α-Arylnitrile **8**	Yield (%)
1	$NCCH_2Li$ **a**	 **a**	>99
2	NCCH(Me)Li **b**	 **b**	>99
3	NCCH(Et)Li **c**	 **c**	>98
4	NCCH(prop)Li **d**	 **d**	85
5	NCCH(Bu)Li **e**	 **e**	71
6	$(CN)_2CHLi$ **f**	 **f**	73
7	$NCCH_2CH(CN)Li$ **g**	 **g**	60
8	PhCH(CN)Li **h**	 **8 h**	71

We first studied the effect of the nature of the trapping reagent on the product distribution using iodobenzene (**9a**) and MeOD as electrophilic precursors. Thus, when the reaction of benzyne (**5**) with 2-lithioacetonitrile (**7a**) (entry 1) was trapped with iodobenzene (**9a**) (which was added prior to benzyne generation at $-30^{\circ}C$), a 1 : 1 mixture of 2-iodophenylacetonitrile (**10a**) and 2-iodophenylacetonitrile (**10b**) was obtained. However, when **5** was treated with **7b** and subsequently quenched with MeOD, compound **10c** was obtained in 99% yields. The structure of **10c** was confirmed by the appearance of a singlet for the methyl hydrogens in its ^1H NMR spectrum.



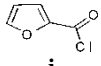
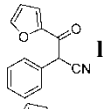
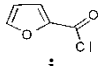
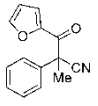
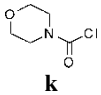
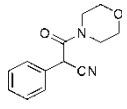
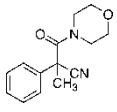
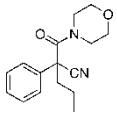
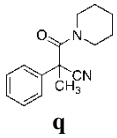
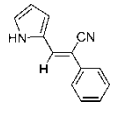
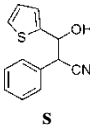
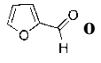
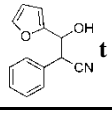
Scheme 2.

Table 2. Electrophilic trapping reactions yielding **10**

Entry	**7** R	Trapping agent **9**	Trapped nitrile **10**	Yield (%)
1	H	PhI **a**	 **a**  **b**	36 36
2	Me	MeOD **b**	 **c**	99
3	H	 **c**	 **d**	78
4	Me	 **d**	 **e**	60
5	Et	 **e**	 **f**	67
6	H	 **f**	 **g**	81
7	Me	 **f**	 **h**	79
8	H	 **g**	 **i**	84
9	H	 **i**	 **j**	71
10	Me	 **i**	 **k**	*c*

(*continued*)

Table 2. Continued

Entry	**7** R	Trapping agent **9**	Trapped nitrile **10**	Yield (%)
11	H	 **j**	 **l**	68
12	Me	 **j**	 **m**	79
13	H	 **k**	 **n**	81
14	Me	 **k**	 **o**	79
15	$CH_3CH_2CH_2$	 **k**	 **p**	82
16	Me	 **l**	 **q**	79
17	H	 **m**	 **r**	78
18	H	 **n**	 **s**	*a*
19	H	 **o**	 **t**	*b*

[a]Compound **10s** was prepared by $NaBH_4$ reduction of **10j** in 91% yield.
[b]Compound **10t** was prepared by $NaBH_4$ reduction of **10l** in 77% yield.
[c]Compound **10k** was not formed; only α-arylnitrile **8b** was obtained.

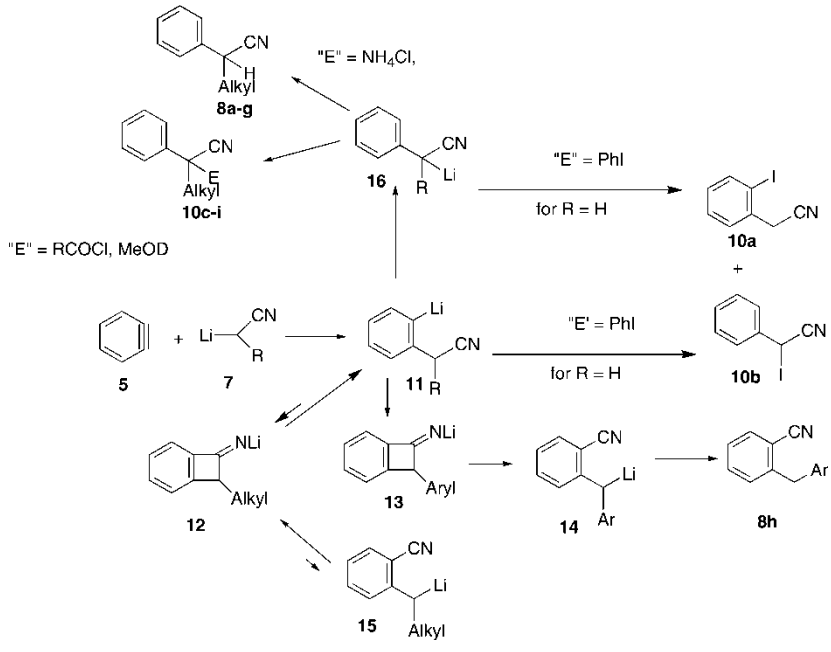
This indicated that the initially formed aryne–nitrile anion, which possesses a negative charge on the carbon adjacent to the cyano-containing side chain adduct (**11**), isomerized to the 2-lithionitrile (**16**) during the course of the reaction (see Scheme 2).

When the reactions of **5** with 2-phenylacetonitriles (**7a**–*c*) were trapped with acid chlorides (**9c**–*m*) (entries 3–17) the respective *β*-keto nitriles **10d**–*r* were obtained in overall yields of 60–84%. Many of the products are known compounds. The structures of the novel compounds were ascertained by ^{1}H NMR, ^{13}C NMR, and elemental analysis. The reactions involving 2-lithioacetonitrile produced 3-ketonitriles. This rapid one-pot synthesis of the 3-ketonitriles under mild conditions, with one exception,[19] is superior to other methods that require harsher conditions (e.g., the synthesis of **10 g** [entry 6] requires heating at 65°C for 2 days)[20,21] and/or are limited to the synthesis of *β*-ketonitriles unsubstituted at the 2-position.[22] In the exceptional case,[19] primary and secondary nitriles are acylated with *N*-acylbenzotriazoles, which are prepared from carboxylic acids. The nitriles are deprotonated using either *n*-butyllithium at −78°C or *t*-BuOK in DMSO at 25°C. In the former case, *N*-acylbenzotriazoles are added, and resulting solution is stirred at −78°C for 2 h, then warmed to room temperature. In the latter case, the triazoles are added, and the resulting solution is stirred an additional 12 h. Although these procedures give slightly higher yields, the procedure reported here has the advantages of using acid chlorides, many of which are commercially available, and a quicker reaction time.

Unfortunately, attempts to trap the reaction of **5** and **7a** with heteroaromatic aldehydes **9n** and **9o** failed to give the corresponding nitrile alcohols **10s** and **10t** (entries 18 and 19). However, these alcohols were obtained by reduction of **10j** and **10l** with $NaBH_4$ in 91% and 77% yields, respectively.

Interestingly, when the reaction of **5** and **7a** was trapped with 1-*H*-pyrrole-2-carbonyl chloride (**9 m**), *Z*-2-phenyl-3-1-*H*-pyrrol-2-yl)acrylonitrile (**10r**) was obtained in 78% (entry 17). Apparently, under these conditions, the latter was obtained by hydrolysis of the corresponding alcohol.

Our studies reported herein support the mechanism put forth by Meyers[23] and further refined by Durst.[24] As shown in Scheme 3, benzyne (**5**) reacts with **7** to give the initial adduct **11**, which closes to the N-lithiobenzocyclobutanimine intermediate **12** in the case of R = alkyl or to **13** in the case of R = Ph. Durst has shown that all benzyne reactions involving nitrile anions proceed through the four-membered ring intermediate **12** or **13**.[24] Furthermore, the direction of opening of **12** and **13** is governed by the relative stability of resulting open chain anions. In the case of **13** (R = phenyl), the ring opens to the more stable rearranged nitrile **14** in which the negative charge is delocalized over two aromatic rings. Proton quench **14** with ammonium chloride then gives **8 h**. However, the intermediate ring **12** (R = alkyl) reverts back to **11** rather than to the rearranged anion **15**. In this case, rearranged anion **15** is less stable than **11** because the negative charge on the 2-carbon in **15** is destabilized by the alkyl electron-donating group.

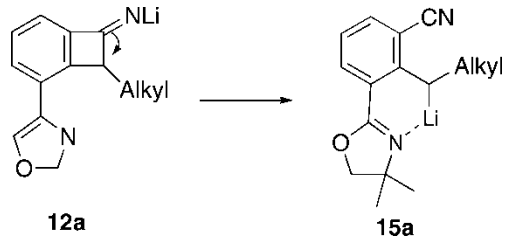


Scheme 3.

As the reaction proceeds, **11** isomerizes to the more stable anion **16**, which is stabilized by resonance interactions between the adjacent phenyl and CN groups. Thus when the PhI electrophile is added to the reaction mixture prior to benzyne formation, both **11** and **16** are trapped by PhI to give **10a** and **10b**, respectively. However, when the trapping agent is added at the end of the reaction, compound **11** completely isomerizes to **16**, which then is trapped by the acid chloride to give the products **10c**–*i*.

This mechanism also provides an explanation of why Meyer's method gives rearranged nitriles rather than typical aryne products from the reaction of 2-lithiated alkanenitriles. As shown in the Scheme 4, the N-lithiobenzocyclobutanimine intermediate **12a** formed in the reaction of 3-oxazolidinyl-substituted benzynes preferentially opens to the rearranged anion **15a** because of a stabilizing complex-induced proximity effect (CIPE)[25] effect between the lithium ion and nitrogen atom of the oxazoline ring.

In conclusion, we have developed a convenient, one-pot, high-yield synthesis of 2-aryl-substituted nitriles and dinitriles that involves generating arynes under neutral conditions in the presence of preformed 2-lithiated nitriles. The yields of these reactions are significantly higher than those prepared under base-mediated benzyne reactions. In addition, several 3-keto-2-arylnitriles were obtained in good overall yields when benzyne was similarly generated and trapped with acid chlorides.



Scheme 4.

EXPERIMENTAL

Melting points and boiling points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^{1}H and ^{13}C NMR spectra were recorded on a 400-MHz Bruker Advance DRX-400 multinuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. Elemental analysis was obtained from Southern Methodist University Analytical Service Laboratories. All chemicals were purchased from Fisher Scientific, VWR, or Aldrich Chemicals.

General Procedure for the Synthesis of 2-Arylnitriles and 2-Aryldinitriles

To a well-stirred solution of THF (5 mL) and n-BuLi (1.6 M, 1.2 eq) kept at $-78^{\circ}C$, a solution of nitrile (1.5 eq) or dinitrile in THF (5 mL) was slowly added through needle syringe system. After stirring for 15 min at that temperature, the solution was allowed to warm at $-40^{\circ}C$. Then a solution of (phenyl)-[*o*-(trimethylsilyl)phenyl]iodonium triflate (0.5 g, 1.0 mmol) in superdry THF (5 mL) was added dropwise followed by Bu_4NF (1.0 M, 1.3 mL, 1.4 eq.). Then the solution was allowed to warm at $0^{\circ}C$ and kept for 15 min. After stirring for another 40 min at rt, a solution of ammonium chloride (1 g/ mL H_2O) was added. The resulting solution was extracted with dichloromethane (2×5 mL), washed with brine, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude compound, which was then purified by column chromatography using ethyl acetate–hexane (9 : 1, v/v) as eluent. All the products reported were synthesized following the same procedure.

Data

Phenyl-acetonitrile (8a). This compound is commercially available.

2-Phenyl-propionitrile (8b). This compound is commercially available.

2-Phenyl-butyronitrile (8c). This compound is commercially available.

2-Phenyl-pentanenitrile (8d). Separated as brownish oil. The ^{1}H NMR and ^{13}C NMR spectra are similar to those previously reported.[19]

2-Phenyl-hexanenitrile (8e). Separated as colorless gummy liquid. The ^{1}H NMR and ^{13}C NMR spectra are similar to those previously reported.[26,27]

2-Phenyl-malononitrile (8f).[19] Separated as reddish brown gummy liquid. The ^{1}H NMR and ^{13}C NMR spectra are similar to those previously reported.

2-Phenyl-succinonitrile (8 g). Separated as reddish color oil. The ^{1}H NMR and ^{13}C NMR spectra are similar to those previously reported.[3]

2-Benzyl-benzonitrile (8 h). Brown-colored gummy liquid. The ^{1}H NMR and ^{13}C NMR spectra are similar to those previously reported.[18]

General Procedure for Trapping 2-Lithio-arylacetonitriles

The reactions were carried out as described for the synthesis of **8** with the exception that the resulting reaction mixture was treated with an appropriate trapping reagent at 0°C, and the resulting solution was stirred an additional 30 min.

Physical and Spectral Properties of the Products (10)

3-Oxo-2-phenyl-butyronitrile (10d). Separated as yellowish crystalline solid, mp 78–79°C. ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H, —CH_3), 4.7 (s, 1H, -CH-), 7.42–7.44 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): δ 27.3 (CH_3) 51 (CH), 116.5 (CN), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.7 (CH), 129.8 (C), 130.0 (CH), 196.8 (C═O). Anal. calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.64; H, 5.77; N, 8.91.

2-Methyl-3-oxo-2-phenyl-butyronitrile (10e). Separated as reddish gummy liquid. ^{1}H NMR ($CDCl_3$): δ 1.83 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 7.34–7.50 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): δ 15.3 (CH_3), 21.8 (CH_3), 54.1 (c), 116.5 (CN), 128.7 (CH), 128.9 (CH), 129.5 (CH), 129.6 (CH), 129.9 (CH), 137.5 (C), 199.1 (C). Anal. calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.45; H, 6.45; N, 8.15.

2-Ethyl-3-oxo-2-phenyl-butyronitrile (10f). Separated as reddish gummy liquid. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H, -CH_3), 2.21–2.25 (m, 2H, -CH_2-), 2.28 (s, 3H, -CH_3) 7.27–7.67 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): δ 8.0 (CH_3), 18.3 (CH_3), 22.1 (CH_2), 56.3 (C), 116.3 (CN), 125.3 (CH), 128.4 (CH), 139.3 (C), 199.1 (C). Anal. calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.88; H, 7.15; N, 7.50.

3-Oxo-2,3-diphenylpropionitrile (10 g). Separated as colorless gummy oil. ^{1}H NMR ($CDCl_3$): δ 5.62 (s, 1H, -CH), 7.39–7.50 (m, 7H, aromatic), 7.61 (dd, $J = 7.6$, 7.8 Hz, 1H aromatic), 7.97 (d, $J = 7.9$ Hz, 2 H, aromatic). ^{13}C NMR ($CDCl_3$): δ 47.1 (CH), 116.9 (CN), 128.7 (CH), 129.1 (CH), 129.4 (CH), 129.6 (CH), 129.8 (CH), 130.1 (CH), 130.8 (C), 134.1 (C), 134.8 (C), 189.3 (C═O). Anal. calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.58; H, 5.06; N, 6.70.

2-Methyl-3-oxo-2,3-diphenyl-propionitrile (10 h). Separated as colorless gummy oil. The ^{1}H NMR and ^{13}C NMR spectra are similar to those reported previously.[19]

3-Oxo-2-phenyl-3-(3,4,5-trimethoxyphenyl)-propionitrile (10i). Separated as colorless low-melting solid. ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3 H, -OMe), 3.84 (s, 3 H, -OMe), 3.88 (s, 3 H, -OMe), 5.64 (s, 1 H, CH), 7.17 (s, 2H, aromatic), 7.36–7.43 (m, 5 H, aromatic). ^{13}C NMR ($CDCl_3$) δ 47.2 (CH), 56.7 (OMex2), 61.4 (OMe), 107.4 (CH), 117.2 (CN), 128.5 (CH), 128.8 (CH), 129.6 (CH), 103.1 (CH), 131.3 (C), 144.0 (C), 153.5 (C), 188.3 (C═O). Anal. calcd. for $C_{19}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.55; H, 5.58; N, 4.61.

3-Oxo-(3-thiophene-2-yl)-propionitrile (10j). Separated as reddish brown gummy liquid. ^{1}H NMR ($CDCl_3$): δ 5.47 (s, 1H, -CH), 7.14 (dd, $J = 4.5$, 4.5 Hz, 1H, aromatic), 7.38–7.43 (m, 3H, aromatic), 7.50 (d, $J = 7.3$ Hz, 2H, aromatic), 7.73 (d, $J = 4.5$ Hz, 1H, aromatic), 7.83 (d, $J = 3.8$ Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 47.9 (CH), 116.8 (CN), 128.6 (CH), 129.1 (CH), 129.6 (CH), 130.0 (CH), 130.8 (C), 134.8 (CH), 136.8 (CH), 140.5 (C), 182.0 (C). Anal. calcd. for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: 68.70; H, 4.02; N, 6.20.

2-Methyl-3-oxo-2-phenyl-(thiophen-2-yl)-propionitrile (10 k). Separated as colorless crystals, mp 65–67°C (lit.[19] 65–67°C).

3-(Furan-2-yl)-3-oxo-2-phenyl)-propionitrile (10l). Separated as yellowish solid. Mp 85–86°C (lit.[24] 89–89.5°C). ^{1}H NMR ($CDCl_3$): δ 5.50 (s, 1H, -CH), 6.60 (s, 1H, aromatic), 7.39–7.41 (m, 4H, aromatic), 7.51 (d, $J = 7.7$ Hz, 2H, aromatic), 7.66 (s, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 46.8 (CH), 113.8 (CH), 116.5 (CN), 120.8 (CH), 128.7 (CH), 129.5 (CH), 129.8 (CH), 130.3 (C), 148.2 (C), 177.8 (C). Anal. calcd. for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 73.97; H, 4.33; N, 6.70.

3-Morpholin-4-yl-3-oxo-2-phenyl)-propionitrile (10n). Separated as yellowish gummy liquid. ^{1}H NMR ($CDCl_3$): δ 2.90–3.04 (m, 2H, -CH_2-), 3.41–3.61 (m, 2H, -CH_2-), 5.67 (s, 1H, -CH-), 7.27–7.61 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): δ 15.3 (CH_2), 31.6 (CH_2), 47.0 (CH), 117.1

(CN), 127.7 (CH), 128.7 (CH), 129.3 (CH), 129.6 (CH), 130.8 (CH), 134.0 (C), 189.4 (C). Anal. calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.90; H, 6.20; N, 12.28.

2-Methyl-3-morpholin-4-yl-3-oxo-2-phenyl)-propionitrile (10o). Separated as colorless gummy liquid. ^{1}H NMR ($CDCl_3$): δ 1.81 (s, 3H, CH_3), 3.01–3.04 (m, 2H, -CH_2-), 3.47–3.66 (m, 6H, -CH_2 X3), 7.33–7.42 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): δ 29.5 (CH_3), 44.1 (CH_2), 47.3 (C), 47.6 (CH_2), 65.7 (CH_2), 66.8 (CH_2), 120.0 (CN), 125.2 (CH), 128.9 (CH), 130.3 (CH), 138.0 (C), 164.0 (C). Anal. calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.99; H, 6.70; N, 11.60.

2-Morpholin-4-carbonyl-2-phenyl-pentanenitrile (10p). Separated as colorless gummy liquid. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, 3H, -CH_3), 1.97–2.4 (m, 2H, -CH_2), 2.9–3.09 (m, 2H, -CH_2), 3.42–3.46 (m, 4H, -CH_2 X2), 7.32–7.42 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): δ 9.8 (-CH_3), 31.4 (-CH_2), 34.4 (-CH_2), 44.1 (-CH_2), 47.5 (-CH_2), 52.9 (C), 65.7 (-CH_2), 66.8 (-CH_2), 119.0 (CN), 125.8 (CH), 128.8 (CH), 129.8 (CH), 136.1 (C), 164.8 (C). Anal. calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.76; H, 7.51; N, 10.42.

2-Methyl-3-oxo-2-phenyl-(3-piperidin-1-yl)-propionitrile (10q). Separated as colorless gummy liquid. ^{1}H NMR ($CDCl_3$): δ 0.86–0.87 (m, 2H, -CH2-), 1.39–1.49 (m, 4H, -CH2-X2), 1.81 (s, 3H, -CH3), 3.17–3.32 (m, 2H, -CH2-), 3.55–3.63 (m, 2H, -CH2-), 7.32–7.39 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): δ 24.4 (CH2), 25.0 (CH2), 25.7 (CH2), 29.8 (CH3), 45.0 (CH2), 47.3 (C), 48.1 (CH2), 120.4 (CN), 125.2 (CH), 128.6 (CH), 129.8 (CH), 138.5 (C), 164.4 (C). Anal. calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.59; H, 7.60; N, 11.60.

(Z)-2-Phenyl-3-(1-*H*-pyrrol-2-yl)-acrylonitrile (10r). Separated as reddish brown gummy liquid. ^{1}H NMR ($CDCl_3$): δ 6.90 (d, $J = 7.8$ Hz, 1H, aromatic), 7.11 (dd, $J = 7.5$, 7.8 Hz, 1H, aromatic), 7.20 (dd, $J = 7.8$, 8.0 Hz, 2H, aromatic), 7.23–7.27 (m, 2H, aromatic), 7.32 (d, $J = 7.8$ Hz, 1H, aromatic), 7.55 (s, 1H, vinylic proton), 7.62 (d, $J = 7.5$ Hz, 1H, aromatic), 10.1 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 108.1 (CH), 113.6 (C), 117.2 (CN), 118.9 (CH), 119.1 (C), 126.3 (CH), 126.5 (CH), 127.7 (CH), 128.5 (CH), 133.9 (C), 140 (CH). Anal. calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: 80.44; H, 5.25; N, 14.50.

3-Hydroxy-2-phenyl-3-(thiophen-2-yl)-propionitrile (10s). Separated as yellowish gummy liquid. ^{1}H and ^{13}C NMR spectra similar as that previously reported. ^{1}H NMR ($CDCl_3$): δ 2.02 (brs, 1H, -OH), 4.76 (d, $J = 6.6$ Hz, 1H, -CH), 5.4–5.5 (m, 1H, -CH-OH), 6.97 (dd, $J = 4.5$, 4.5 Hz, 1H, aromatic), 7.23–7.38 (m, 4H, aromatic), 7.47–7.49 (m, 3H, aromatic). ^{13}C NMR

($CDCl_3$): δ 38.5 (CH), 77.4 (CH-OH), 116.8 (CN), 124.3 (CH), 125.3 (CH), 128.6 (CH), 129.1 (CH), 129.6 (CH), 130.6 (C), 130.8, 134.8 (CH), 136.8 (CH), 146.5 (C). Anal. calcd. for $C_{13}H_{11}NOS$: C, 68.09; H, 4.84; N, 6.11. Found: C, 68.20; H, 4.99; N, 6.15.

3-Hydroxy-2-phenyl-3-furan-2-yl)-propionitrile (10t). Separates as brownish gummy liquid. ^1H NMR ($CDCl_3$): δ 2.25 (brs, 1H, -OH), 4.62 (d, $J = 6.5$ Hz, 1H, -CH-), 5.1–5.6 (m, 1H, -CH-OH), 6.31 (s, 1H, aromatic), 6.60 (s, 1H, aromatic), 7.37–7.51 (m, 5H, aromatic), 7.66 (s, 1H, aromatic). ^{13}C NMR ($CDCl_3$): δ 39.0 (CH), 70.34 (CH-OH), 108.6 (CH), 110.9 (CH), 116.5 (CN), 128.5 (CH), 128.7 (CH), 129.5 (CH), 129.8 (CH), 130.6 (C), 142.9 (CH), 158.5 (C). Anal. calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 7.40; H, 5.25; N, 6.70.

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