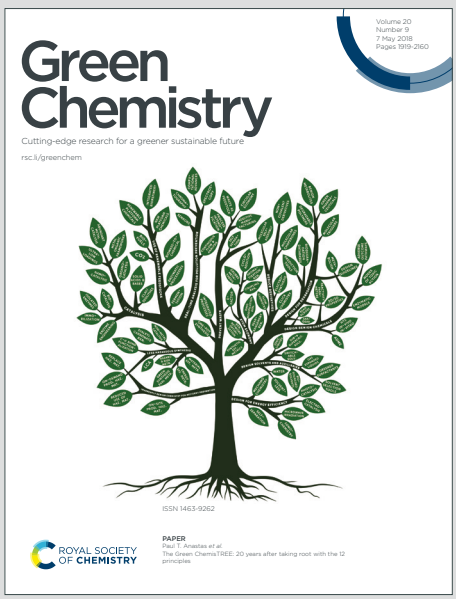
View Article Online
View Journal

Green Chemistry

Cutting-edge research for a greener sustainable future

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: I. Satyanarayana, K. B. Manjappa and D. Yang, *Green Chem.*, 2020, DOI: 10.1039/D0GC03411H.



View Article Online
DOI: 10.1039/D0GC03411H

ARTICLE

Nitromethane as a Surrogate Cyanating Agent: 7-*N*,*N*-Dimethylamino-4-Hydroxycoumarin-Catalyzed, Metal-Free Synthesis of α-Iminonitriles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

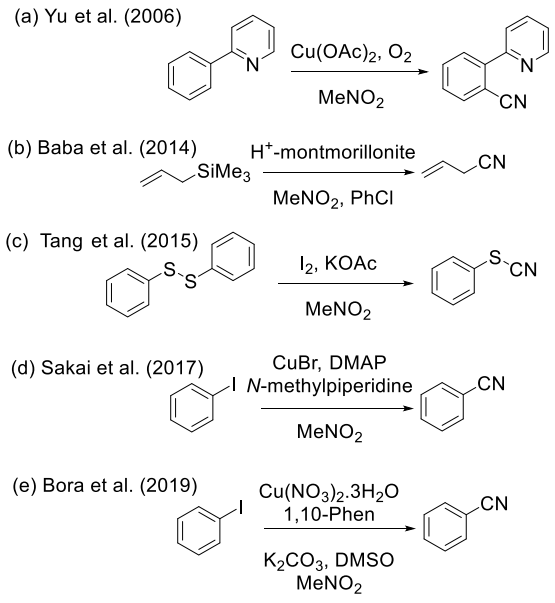
Iddum Satyanarayana,[a] Kiran B. Manjappa[b]* and Ding-Yah Yang[a,b]*

An efficient, metal/alkali-cyanide free approach for the synthesis of α-iminonitriles via kinetically controlled, base-mediated and 1,3-diketone-catalyzed reaction is reported. The preparation of target compounds was realized by condensation of substituted anilines and aldehydes in nitromethane as a surrogate cyanating agent and as a solvent. This strategy was further improved by replacing aldehydes and nitromethane with β-nitrostyrene and ethanol, respectively, rendering the methodology greener. The catalytic role played by 1,3-diketones such as 7-*N*,*N*-dimethylamino-4-hydroxycoumarin in this three-component reaction was investigated, and a plausible mechanism was proposed based on control experiments.

Introduction

Nitriles constitute an integral part of numerous natural products, agrochemicals, secondary metabolites, and active pharmaceutical ingredients.[1-3] They often serve as an essential precursor for the construction of *N*-heterocycles, carbonyl compounds and amines. Owing to nitriles' broad reactivity, exploring the methodologies for efficient cyanation is a long-standing interest of organic chemists.[4] Undoubtedly, hydrogen cyanide is one of the simplest yet impractical reagents to be used for the CN group introduction. Commonly practiced cyanation involves the extensive use of metal cyanides,[5a-d] isocyanide,[5e-h] tosylcyanide,[5i] ethyl cyanoacetate,[5j] TBN (*tert*-butyl nitrite)[5k,l,] and NCTS (*N*-cyano-*N*-phenyl-*p*-toluene sulfonamide).[5m-o] Most of these reagents suffer from high toxicity and thus require stringent precautions while handling. Despite their adverse effect, usage of such toxic, hazardous and lethal reagents has become one of the irreplaceable ways in many synthetic conversions. Therefore, searching for the less toxic and non-metal cyanide-based reagents to function as a surrogate source for cyanide remains highly desired.[6] Although numerous efforts to introduce new non-cyanide reagents such as DMSO[7] and urea[8] for cyanation in the past, those cyanide alternatives were sparingly used in the synthesis.

Nitromethane is used as a solvent as well as a source for carbon, amine and nitrile to construct functional building blocks that can further be employed in various transformations.[9] For instance, Jiao and co-workers have discovered the ability of nitromethane to donate its nitrogen to aldehydes, ketones and alkynes in Schmidt-type amides and the preparation of nitriles.[10] Radosevich et al. have recently reported the versatility of nitromethane as a surrogate for methylamine.[11] For the cases of nitromethane as a CN source, Yu et al. have reported the first example of copper-mediated, chelate-driven arene cyanation with nitromethane back in 2006 (Scheme 1).[12a] Since then, only a few related reactions have been documented (Scheme 1),[12b-e] and most of them required metals as a catalyst. While the construction of C-N bonds via metal-free radical C(sp^3)-H functionalization to avoid the high toxicity of transition metals has been well developed,[13] the metal-free cyanation using nitromethane as a surrogate cyanating source remains to be a challenging task.

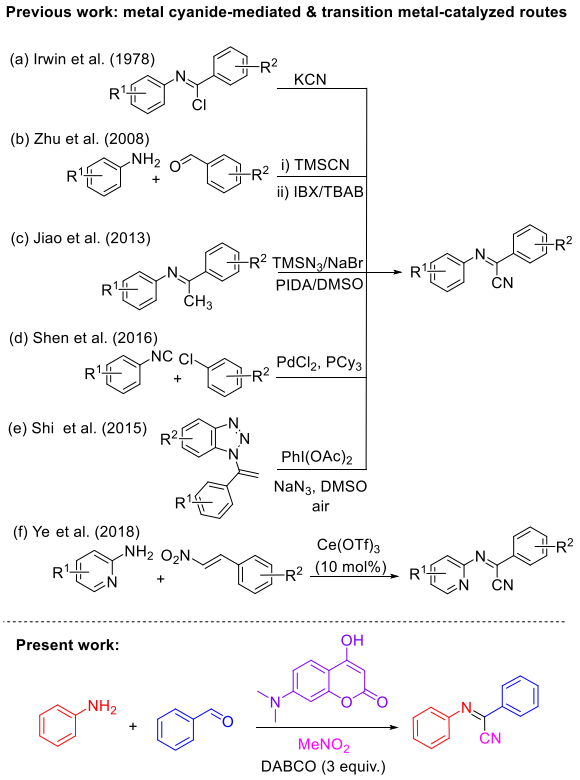


Scheme 1 The previous reports of using nitromethane as a cyanating agent.

[a] Department of Chemistry, Tunghai University, No. 1727, Sec. 4, Taiwan. Boulevard, Xitun District, Taichung 40704, Taiwan
[b] Graduate Program for Biomedical and Materials Science, Tunghai University, No. 1727, Sec. 4, Taiwan Boulevard, Xitun District, Taichung 40704, Taiwan
Email: kiran@thu.edu.tw, yang@thu.edu.tw

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

α-Iminonitriles are the cyano-bearing imines that often serve as precursors for various functional group transformations.[14] Additionally, they can also function as cyanating reagents to introduce the CN group onto arenes.[15] Currently, the most conventional approach to the preparation of α-iminonitriles still resorts to the toxic metal/non-metal cyanide reagents, including KCN,[16a] NaCN,[16b,] TMSCN,[16c] $TMSN_3$,[16d] isocyanides[16e,] and triazole ring-opening[16f,g] pathway (Scheme 2, a–e). Recently, Ye and co-workers[17] have reported the efficient synthesis of pyridine-derived α-iminonitriles via $Ce(OTf)_3$-catalyzed condensation of 2-aminopyridines with nitroalkenes (Scheme 2, f). Although this strategy is metal cyanide-free, it lacks substrate generality since the arylamines are limited to 2-aminopyridines only. Thus, the development of a novel strategy for the preparation of α-iminonitrile under cyanide-free and transition metal-free conditions with broad substrate scope is highly preferable. Herein, a metal/alkali-cyanide free and multicomponent approach to the preparation of structurally diverse α-iminonitriles is reported. The present methodology features the usage of readily available arylamines and aldehydes as the substrates; the dual role of nitromethane as a surrogate cyanating agent and as a solvent. Additionally, considering the toxicity of nitromethane, an effort has been made to limit its use as reagent only by substituting it with environmentally benign solvent ethanol. Furthermore, 1,3-diketones such as 7-*N*,*N*-dimethylamino-4-hydroxycoumarin are employed as an organocatalyst to replace the commonly used transition metals in this transformation. Eventually, the mechanism of this three-component reaction is investigated by performing control experiments as well as isolating the key intermediates.

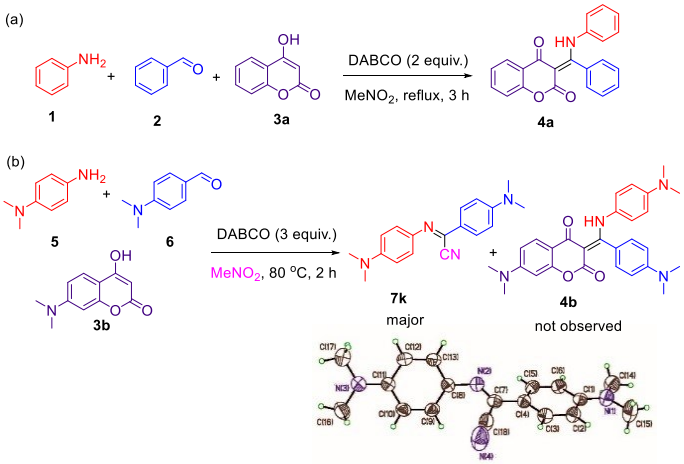


Scheme 2 Previous and present synthesis of α-iminonitriles.

Results and Discussion

View Article Online
DOI: 10.1039/D0GC03411H

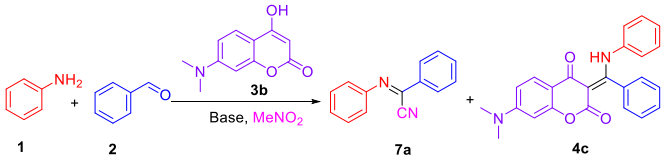
Recently, we have reported an efficient methodology for the preparation of β-enaminone **4a** via a one-pot, three-component reaction of arylamine **1**, aldehyde **2** and 4-hydroxycoumarin (**3a**) using nitromethane as a solvent (Scheme 3, a).[18] During the extensive substrate scope studies, we have serendipitously discovered the formation of α-iminonitrile in the reaction with specific substrates. For example, when a mixture of amine **5**, aldehyde **6** and 7-*N*,*N*-dimethylamino-4-hydroxycoumarin (**3b**) was refluxed in the presence of three equiv. of DABCO as a base in nitromethane, the α-iminonitrile **7k** was obtained as a major product (Scheme 3, b). Surprisingly, the expected β-enaminone **4b** was not observed in this reaction. The spectroscopic and ORTEP crystal analysis unambiguously confirmed the molecular structure of **7k** (Scheme 3).[19]



Scheme 3 Synthesis of β-enaminone **4a** (a) and α-iminonitrile **7k** (b).

Intrigued by the unexpected results and envisaged the importance of α-iminonitriles,[20] we have launched the systematic investigation to discern the formation of α-iminonitriles in terms of the influence of the base, reaction conditions, and the role played by 4-hydroxycoumarin in this MCR. Table 1 summarizes the screening of the optimized conditions for α-iminonitrile formation. The generation of β-enaminone **4c** is ubiquitous in this MCR and could be isolated as the major product when DMAP, TEA, DIPEA, pyridine or Cs_2CO_3 were employed as a base (Table 1, entries 1–7). Nevertheless, the yield of β-enaminone could be minimized through fine-tuning the conditions and thereby enhancing the formation of the desired α-iminonitrile **7a**. For instance, increasing the amount of DABCO from two to three equiv. enhanced the product ratio of α-iminonitrile **7a** to β-enaminone **4c** (Table 1, entries 1 and 8). Further, bringing down the reaction temperature from reflux to 80 °C suppressed the formation of β-enaminone **4c** from 50 to 43% (Table 1, entries 8 and 9). Employing excess of base, lowering the reaction temperature and shortening the reaction time were found to be beneficial to the formation of α-iminonitrile **7a**. Finally, among the bases screened, DABCO was proved to be the most commending one over others for the generation of α-iminonitrile **7a**.

Table 1 Optimization for the formation of α-iminonitrile **7a**.



Entry	Base	Equiv.	Time (h)	Temp. (°C)	Yield (%)	
					7a	**4c**
1[a]	DABCO	2.0	2	reflux	33	67
2	DMAP	2.0	2	reflux	26	37
3	DBU	2.0	2	reflux	5	10
4	TEA	2.0	2	reflux	trace	68
5	DIPEA	2.0	4	reflux	trace	50
6	pyridine	2.0	6	reflux	20	19
7	Cs_2CO_3	2.0	6	reflux	trace	35
8[b]	DABCO	3.0	2	reflux	37	50
9	DABCO	3.0	2	80	41	43
10	DABCO	3.0	4	80	38	51[c]

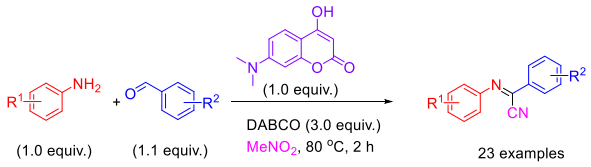
Note [a]Less than 1.0 equiv. of the base resulted in poor conversion; [b]No significant increase for **7a** if more than 3.0 equiv. of base were added. [c]Extended reaction time favored for the formation of β-enaminone.

Since the added coumarin **3b** did not incorporate into the molecular structure of the product α-iminonitriles, the role played by 1,3-diketone in this MCR remained elusive. Several cyclic 1,3-diketones were evaluated for their competence to facilitate the reaction, as shown in Table 2. All four 1,3-diketones employed in the MCR were found to be able to promote product formation with varying extents. Coumarin **3b** with an electron-donating group on benzene moiety gave better yield than the unsubstituted 4-hydroxycoumarin **3a** and dimedone **3d** (Table 2, entries 3–5). An increasing amount of coumarin **3b** from 0.5 to 1.0 equivalent enhanced the formation of α-iminonitrile **7k** from 52 to 74% (Table 2, entries 1–2). Nevertheless, further increments of **3b** failed to influence the yield significantly. Thus, heating of amine and aldehyde in the presence of DABCO (3 equiv.) and coumarin **3b** (1 equiv.) in nitromethane at 80 °C for 2 h was employed as the standard reaction conditions for subsequent substrate scope studies.

Figure 1 lists the structures and yields of the prepared α-iminonitriles **7a–w**. A wide range of functionalized α-iminonitriles could be prepared in moderate to good yields, indicating the reaction has a high tolerance to functional groups. While a lower yield of 41% (**7a**) was recorded in the case of unsubstituted aldehyde and aniline, a significant increase in yield was observed when either an electron-donating or electron-withdrawing substituent was introduced onto aniline or aldehyde. For instance, the introduction of an electron-donating group on the substrates aldehyde and amine rendered good yields up to 74% (**7k**). A similar phenomenon was also observed when an electron-withdrawing group was introduced, implying the yield of this MCR was critically influenced by the inductive effect. Moreover, the reaction also worked well for other heteroaromatic scaffolds such as quinoline (**7j**), pyridine (**7i**, **7s**, **7t**) and thiophene (**7v**, **7w**). When an alkyl amine or aldehyde was employed as the substrate, the reaction predominately gave the β-enaminones. Hence, this methodology worked only for the aryl system.

Table 2 Screening of 1,3-diketones **3a–d**.

Entry	1,3-Diketone	Equiv.	**7k** (Yield %)
1	7-*N*,*N*-dimethylamino-4-hydroxycoumarin (**3b**)	0.5	52
2	7-*N*,*N*-dimethylamino-4-hydroxycoumarin (**3b**)	1	74
3	7-*N*,*N*-dimethylamino-4-hydroxycoumarin (**3b**)	2	76
4	dimedone (**3d**)	1	10
5	4-hydroxycoumarin (**3a**)	1	27
6	7-*N*,*N*-diethylamino-4-hydroxycoumarin (**3c**)	1	68



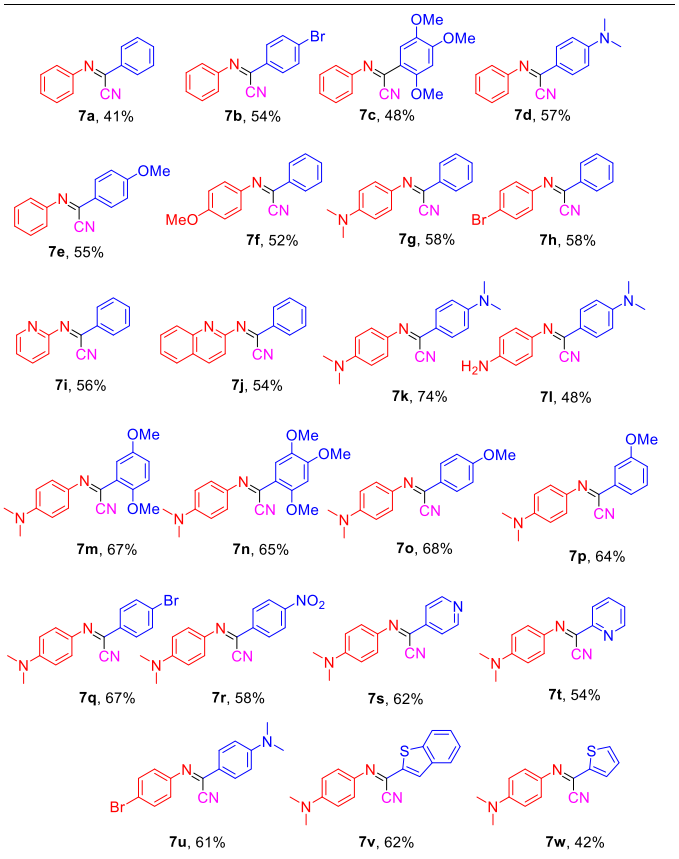
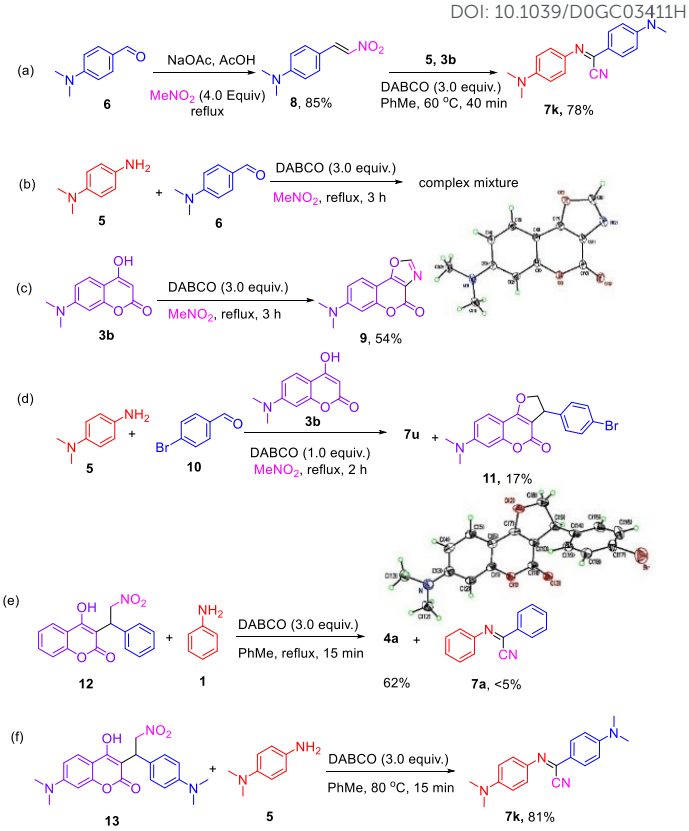


Figure 1 Structures and yields of the prepared α-iminonitriles **7a–w**.

View Article Online
DOI: 10.1039/D0GC03411H

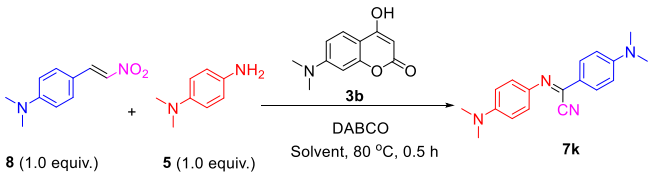
To gain insights into the mechanism of this reaction and the role played by coumarin **3b**, a series of control experiments were designed and performed, as shown in Scheme 4. Condensation of aldehyde **6** and nitromethane gave the corresponding Henry product **8** (β-nitrostyrene) under reflux conditions (Scheme 4, a). The subsequent reaction of **8** with amine **5** and coumarin **3b** under standard conditions generated α-iminonitrile **7k** in good yield (78%). Interestingly, when aniline **5** and aldehyde **6** were heated in nitromethane in the absence of coumarin **3b**, a complex mixture was observed, and no expected α-iminonitrile was detected (Scheme 4, b). This observation suggests that coumarin **3b** is indispensable for α-iminonitrile formation. It is worth mentioning that heating of coumarin **3b** alone in nitromethane under standard conditions gave the coumarin-fused oxazole **9** as the major product (Scheme 4, c). In an attempt to isolate the possible intermediates from the reaction, *p*-bromobenzaldehyde (**10**) was reacted with aniline **5** and coumarin **3b** in nitromethane in the presence of only one equiv. of DABCO. Luckily, the 2,3-dihydrofuro[3,2-*c*]coumarin **11** was isolated in 17% yield in addition to the expected α-iminonitrile **7u** (Scheme 4, d). The X-ray crystallography studies further confirmed the molecular structure of **11** (see the SI). The isolation of **11** prompted us to believe that the Michael adduct **12** might be one of the intermediates in this reaction since **11** was likely to be formed by intramolecular cyclization of **12** through the removal of HNO_2. To further validate this hypothesis, two putative intermediates **12** and **13** were prepared by the coupling of 4-hydroxycoumarins with β-nitrostyrene according to the literature procedure.[21] When the prepared **12** was refluxed with aniline **1** and DABCO (3.0 equiv.) in toluene for 15 min, the β-enaminone **4a** was isolated as the major product in 62% along with a trace amount of α-iminonitrile **7a** (Scheme 4, e). Preparation of pure **13** proved to be difficult since it could not be separated from the starting material coumarin **3b**. The inseparable mixture of **13** and **3b** was then heated with aniline **5** and DABCO (3.0 equiv.) in toluene at 80 °C for 15 min. To our delight, a complete conversion of **13** into the corresponding α-iminonitrile **7k** was observed, and no trace of the corresponding β-enaminone was detected (Scheme 4, f). Hence, our studies indicate that compounds **12** and **13** are indeed the intermediates for these three-component reactions, whereas coumarin **3b** serves as a sacrificial agent in generating the α-iminonitriles.



Scheme 4 Control experiments.

From control experiments, we discovered that the readily available Henry product **8** can serve as an alternate substrate to react with amine **5** in toluene, leading to the generation of α-iminonitrile **7k** without utilizing nitromethane as a solvent. This finding prompted us to further investigate the reaction conditions to reduce the use of excessive nitromethane, rendering the process greener. Table 3 summarizes the optimization reactions of β-nitrostyrene **8** and amine **5** in the presence of coumarin **3b** as a catalyst under various conditions. During the screening process, a pronounced solvent effect on the formation of α-iminonitrile **7k** was observed. That is, a non-polar aromatic solvent like toluene enhanced the formation of α-iminonitrile **7k** (Table 3, entry 1; 78%), whereas polar aprotic solvents such as ACN, dioxane and THF inhibited it (Table 3, entries 2–4). To our delight, when the reaction was performed in a protic solvent such as EtOH, the yield of **7k** rose to 82% along with the recovery of 20% of coumarin **3b** (Table 3, entry 5). Besides, the loadings of coumarin **3b** and DABCO were also screened. Our studies indicate that the yield of **7k** was proportional to the loadings of coumarin **3b** (Table 3, entries 5–7), and a decreasing amount of DABCO loadings resulted in lower product conversion (Table 3, entries 7–9). As for the temperature effect, a limited amount of product formation was detected even when the reaction was carried out at room temperature. Nevertheless, prolonged reaction time at that temperature led to the formation of a complex mixture. The increase of reaction temperature enhanced the product formation with maximum yield at 80 °C for 30 min (**7k**, 82%).

Table 3 Optimization for the formation of α-iminonitrile **7k**.

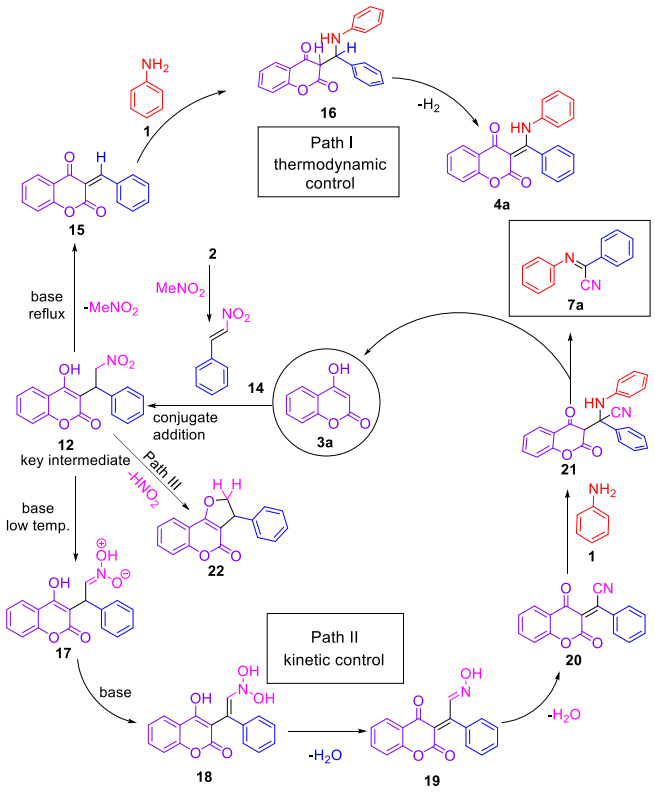


Entry	Solvent	DABCO (equiv.)	3b (equiv.)	7k (Yield %)	3b Recovery (%)
1	PhMe	3.0	1.0	78	trace
2	ACN	3.0	1.0	10	<5
3	dioxane	3.0	1.0	42	trace
4	THF	3.0	1.0	36	trace
5	EtOH	3.0	1.0	82	20
6	EtOH	3.0	0.5	64	10
7	EtOH	3.0	0.3[b]	38	5
8	EtOH	2.0	1.0	58	<10
9[a]	EtOH	1.0	1.0	26	<5

Note: [a]reaction did not reach completion; [b]decrease the loading of **3b** resulted in less yield of **7k**.

The optimization of the reaction between Henry product **8** and amine **5** in ethanol has certainly brought a greener approach to the preparation of α-iminonitriles **7k**. This modified strategy has not only aided in moderately enhancing the yield (74% to 82%) but also partially recovering of coumarin **3b**. Hence, several previously synthesized α-iminonitriles (Figure 1, **7a**, 41%; **7c**, 48%; **7l**, 48%) were re-prepared by this modified methodology. As expected, cleaner conversion along with improved yields were observed (**7a**, 45%; **7c**, 58%; **7l**, 56%). To further expand the scope of this reaction, some alkylamines and alkyl Henry products were examined to test their compatibility. Unfortunately, all attempts failed to yield any corresponding alkyl-substituted α-iminonitriles, which is a limitation of the present methodology.

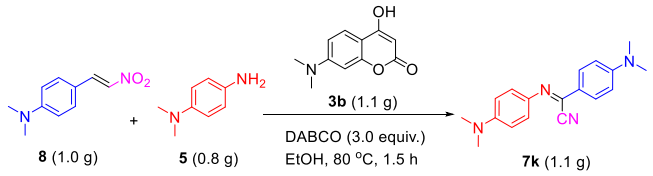
Based on the crucial information retrieved from the control experiments along with the isolation of the putative reaction intermediate, a plausible mechanism for the preparation of β-enaminone **4a** and α-iminonitrile **7a** is proposed (Scheme 5). The initiation of the reaction starts with the formation of Henry product **14** by the condensation of aldehyde **2** and nitromethane. The subsequent attack by coumarin **3a** onto **14** via Michael addition presumably yield the adduct **12**. We envision that compound **12** might be the key intermediate leading to the formation of either β-enaminone **4a** or α-iminonitrile **7a**, depending upon the reaction conditions. For instance, under reflux conditions (Path I, thermodynamic control), the adduct **12** undergoes nitromethane elimination to furnish the α,β-unsaturated ketone **15**. The subsequent conjugate addition of aniline **1** to **15** generates the compound **16**. Final oxidative dehydrogenation results in the formation of the β-enaminone **4a**. On the other hand, at a lower temperature (Path II, kinetic control), the adduct **12** proceeds to a base-mediated isomerization to yield compound **18** through iminium oxide **17**. Compound **18** then undergoes sequential dehydration or vinylogous elimination[22] of water via the oxime **19** to afford the nitrile **20**. Similar to that of α,β-unsaturated ketone **15**, we believe that the nitrile **20** is also highly susceptible to nucleophilic attack by aniline **1** to give the tetrahedral intermediate **21**. Final expulsion of coumarin **3a** from **21** furnishes the target α-iminonitrile **7a**.



Scheme 5 Plausible mechanism for the formation of β-enaminone **4a** and α-iminonitrile **7a**.

In the course of the formation of α-iminonitrile **7a**, coumarin **3a** is proposed to function as an organocatalyst, which at first serves as a nucleophile to trap Henry product **14** at the initial stage of the reaction. However, at the later stage of the reaction, coumarin **3a** acts as a leaving group by being expelled from the tetrahedron intermediate **21**. Nevertheless, due to the competitive reactions such as the formation of β-enaminone **4a**, 2,3-dihydrofuro[3,2-*c*]coumarin **22** and coumarin-fused oxazole **9**, a stoichiometric rather than catalytic amount of coumarin **3a** is required for this MCR.

To demonstrate the feasibility of a large scale preparation of α-iminonitriles by the modified methodology, a gram-scale reaction for the preparation of α-iminonitrile **7k** was carried out, as shown in Scheme 6. Hence, 1.0 g of β-nitrostyrene **8** (1 equiv.) was reacted with 0.8 g of amine **5** (1.1 equiv.) and 1.1 g of coumarin **3b** (1 equiv.) in EtOH (20 mL) under standard reaction conditions. As a result, 1.1 g of α-iminonitrile **7k** (72%) was obtained, indicating that the reaction yield did not compromise markedly by a large-scale synthesis. Further, 182 mg (17%) of catalyst **3b** was recovered from the reaction.



Scheme 6. Gram-scale preparation of α-iminonitrile **7k**.

To the best of our knowledge, this synthesis of α-iminonitrile from arylamine and aldehyde represents the first example which employs nitromethane as a surrogate cyanating agent under metal-free conditions. Likewise, for the first time, cyclic 1,3-diketone, that is, 7-*N*,*N*-dimethylamino-4-hydroxycoumarin is utilized to function as an organocatalyst to catalyze organic reactions.

Conclusions

In summary, we have demonstrated that α-iminonitriles can be constructed via 7-*N*,*N*-dimethylamino-4-hydroxycoumarin-catalyzed condensation of anilines and aromatic aldehydes using nitromethane as a surrogate cyanating agent. The scope of this cyanide/metal-free reaction was illustrated by the preparation of 23 α-iminonitrile analogues with moderate to good yields along with good functional group tolerance. Alternately, the target compounds could also be prepared by direct coupling of β-nitrostyrenes with anilines in the presence of a coumarin catalyst in ethanol. Our studies suggested that product formation is favored under kinetically controlled conditions and facilitated by 1,3-diketones such as 7-*N*,*N*-dimethylamino-4-hydroxycoumarin. Further, the application of this quasi-pioneering activation of nitromethane and 1,3-diketone-catalyzed reaction to the synthesis of other organic molecules is currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment.

We thank the Ministry of Science and Technology of the Republic of China, Taiwan, for financially supporting this research under Contract No. MOST 108-2113-M-029-001.

Notes and references

1 F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem*., 2010, **53**, 7902–7917.
2 F. F. Fleming, *Nat. Prod. Rep*., 1999, **16**, 597–606.
3 C. A. Tolman, R. J. McKinney, W. C. Seidel, J. D. Druliner and W. R. Stevens, *Adv. Catal*., 1985, **33**, 1–46.
4 (a) C. Qin and N. Jiao, *J. Am. Chem. Soc*., 2010, **132**, 15893–15895; (b) T. Wang and N. Jiao, *J. Am. Chem. Soc*., 2013, **135**, 11692–11695; (c) T. Shen, T. Wang, C. Qin and N. Jiao, *Angew. Chem., Int. Ed*., 2013, **52**, 6677–6680; (d) X. Zong, Q. Z. Zheng and N. Jiao, *Org. Biomol. Chem*., 2014, **12**, 1198–1202.
5 (a) A. V. Ushkov and V. V. Grushin, *J. Am. Chem. Soc.,* 2011, **133**, 10999–11005; (b) R. K. Arvela and N. E. Leadbeater, *J. Org. Chem.,* 2003, **68**, 9122–9125; (c) X. Jia, D. Yang, S. Zhang and J. Cheng, *Org. Lett.,* 2009, **11**, 4716–4719; (d) B. V. S. Reddy, Z. Begum, Y. J. Reddy and J. S. Yadav, *Tetrahedron Lett*., 2010, **51**, 3334–3336; (e) S. Xu, X. Huang, X. Hong and B. Xu, *Org. Lett*., 2012, **14**, 4614–4617; (f) J. Peng, J. Zhao, Z. Hu, D. Liang, J. Huang and Q. Zhu, *Org. Lett*., 2012, **14**, 4966–4969; (g) X. Hong, H. Wang, G. Qian, Q. Tan and B. Xu, *J. Org. Chem*., 2014, **79**, 3228–3237; (h) X. Jiang, J. M. Wang, Y. Zhang, Z. Chen, Y. M. Zhu and S. J. Ji, *Tetrahedron*, 2015, **71**, 4883–4887; (i) S. Kamijo, T. Oshikawa and M. Inoue, *Org. Lett*., 2011, **13**, 5928–5931; (j) S. Zheng, C. Yu and Z. Shen, *Org. Lett*., 2012, **14**, 3644–3647; (k) Z. Shu, Y. Ye, Y. Deng, Y. Zhang and J. Wang, *Angew. Chem*., *Int. Ed*. 2013, **52**, 10573–10576; (l) D. Tsuchiya, Y. Kawagoe, K. Moriyama and H. Togo, *Org. Lett*., 2013, **15**, 4194–4197; (m) T. J. Gong, B. Xiao, W. M. Cheng, W. Su, J. Xu, Z. Liu, L. Liu and Y. Fu, *J. Am. Chem. Soc*., 2013, **135**, 10630–10633; (n) M. Chaitanya, D. Yadagiri and P. Anbarasan, *Org. Lett*., 2013, **15**, 4960–4963; (o) Y. Yang and S. L. Buchwald, *Angew. Chem*., *Int. Ed*., 2014, **53**, 8677–8681.
6 For a recent review on non-toxic cyanation agents, see: M. N. Alexander and T. Opatz, *Org. Biomol. Chem*., 2019, **17**, 11–23.
7 X. Ren, J. Chen, F. Chen and J. Cheng, *Chem. Commun*., 2011, **47**, 6725–6727.
8 K. Zheng, B. Liu, S. Chen and F. Chen, *Tetrahedron Lett*., 2013, **54**, 5250–5252.
9 X. Qi, J.-B. Peng and X.-F. Wu, in *Solvents as Reagents in Organic Synthesis: The Applications of Nitromethane as Reagent and Solvent in Organic Synthesis*, ed. Wiley-VCH Verlag GmbH & Co. KGaA. 2018, 377–402.
10 J. Liu, C. Zhang, Z. Zhang, X. Wen, X. Dou, J. Wei, X. Qiu, S. Song and N. Jiao, *Science*, 2020, **367**, 281–285.
11 G. Li, Z. Qin and A. T. Radosevich, *J. Am. Chem. Soc.* 2020, **142**, 16205–16210.
12 (a) X. Chen, X. S. Hao, C. E. Goodhue and J. Q. Yu, *J. Am. Chem. Soc*., 2006, **128**, 6790–6791; (b) K**.** Motokura, K**.** Matsunaga, A**.** Miyaji, S**.** Yamaguchi and T. Baba, *Tetrahedron Lett*., 2014, **55**, 7034–7038 ; (c) Z.-H. Wang, X.-M. Ji, M.-L. Hub and R.-Y. Tang, *Tetrahedron Lett*., 2015, **56**, 5067–5070; (d) Y. Ogiwara, H. Morishita, M. Sasaki, H. Imai, and N. Sakai, *Chem. Lett.* 2017, **46**, 1736–1739; (e) R. Saikia, S. D. Baruah, R. C. Deka, A. J. Thakur and U. Bora, *Eur. J. Org. Chem*., 2019, **36**, 6211–6216.
13 S.-Z. Song, Y.-N. Meng, Q, Li and W. T. Wei, *Adv. Synth. Catal*., 2020, **362**, 2120–2134.
14 Application of α-iminonitriles: (a) A. Roychowdhury, V. V. Kumar and A. P. Bhaduri, *Synth. Commun*., 2006, **36**, 715–727; (b) X. You, X. Xie, R. H. Sun, H. Y. R. Chen, S. Li and Y. H. Liu, *Org. Chem. Front*., 2014, **1**, 940–946; (c) R. Surmont, B. De Corte and N. De Kimpe, *Tetrahedron Lett*., 2009, **50**, 3877–3880; (d) A. V. Varlamov, D. G. Grudinin, A. A. Eganov, A. I. Chernyshev and A. N. Levov, *Chem. Heterocycl. Compd*., 2005, **41**, 872–876; (e) P. Sarnpitak and M. Krasavin, *Tetrahedron*, 2013, **69**, 2289–2295.
15 α-Iminonitriles as cyanating agents: (a) Z. B. Chen, F. L. Zhang, Q. Yuan, H. F. Chen, Y. M. Zhu and J. K. Shen, *RSC Adv*., 2016, **6**, 64234–64238; (b) Z. Chen, P. Liang, B. Liu, H. Luo, J. Zheng, X. Wen, T. Liua and M. Ye, *Org. Biomol. Chem*., 2018, **16**, 8481–8485; (c) Y. L. Shi, Q. Yuan, Z. B. Chen, F. L. Zhang, K. Liu and Y. M. Zhu, *Synlett*, 2018, **29**,

View Article Online
DOI: 10.1039/D0GC03411H

359–363; (d) N. R. Rondla, J. M. Ogilvie, Z. Pan and C. J. Douglas, *Chem. Commun*., 2014, **50**, 8974–8977.

16 (a) J. G. Smith and D. C. Irwin, *Synthesis,* 1978, 894; (b) B. S. Jursic, F. Douelle, K. Bowdy and Ed. D. Stevens, *Tetrahedron Lett.,* 2002, **43**, 5361–5365; (c) P. Fontaine, A. Chiaroni, G. Masson and J. Zhu, *Org. Lett.*, 2008, **10**, 1509–1512; (d) F. Chen, X. Huang, Y. Cui and N. Jiao, *Chem. Eur. J.,* 2013, **19**, 11199–11202; (e) Z. B. Chen, Y. Zhang, Q. Yuan, F. L. Zhang, Y. M. Zhu and J. K. Shen, *J. Org. Chem.,* 2016, **81**, 1610–1616; (f) Y. Su, J. L. Petersen, T. L. Gregg and X. Shi, *Org. Lett.,* 2015, **17**, 1208–1211; (g) A. H. Kalbandhe, A. C. Kavale and N. N. Karade, *Eur. J. Org. Chem*., 2017, 1318–1322.

17 Z. Chen, P. Liang, J. Zheng, Z. Zhou, X. Wen, T. Liu and M. Ye, *ACS Omega*, 2018, **3**, 12520–12529.

18 W. C. Hsieh, K. B. Manjappa and D. Y. Yang, *RSC Adv*., 2019, **9**, 34088–34094.

19 Crystallographic data (excluding structure factors) for **7k**, **9** and **11** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-2023156, 2023155 and 2023154, respectively.

20 (a) J. J. Garcia, N. M. Brunkan and W. D. Jones, *J. Am. Chem. Soc*., 2002, **124**, 9547–9555; (b) Y. Nakao, A. Yada, S. Ebata and T. Hiyama, *J. Am. Chem. Soc*., 2007, **129**, 2428–2429; (c) M. Tobisu, Y. Kita, Y. Ano, N. Chatani, *J. Am. Chem. Soc*., 2008, **130**, 15982–15989; (d) D. G. Yu, M. Yu, B. T. Guan, B. J. Li, Y. Zheng, Z. H. Wu and Z. J. Shi, *Org. Lett*., 2009, **11**, 3374–3377; (e) Y. Kita, M. Tobisu, N. Chatani, *Org. Lett*., 2010, **12**, 1864–1867.

21 D. K. Barange, V. Kavala, C. W. Kuo, P. M. Lei and C. F. Yao, *Tetrahedron*, 2011, **67**, 2870–2877.

22 N. M. Moreira, L. S. R. Martelli, K. I. R. de Julio, J. Z. Schpector, T. Opatz, and A. G. Corrêa, *Eur. J. Org. Chem*., 2020, **29**, 4563–4570.