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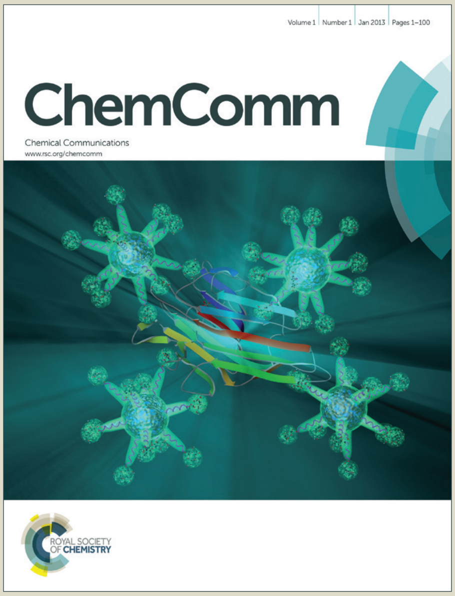

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Journal Name

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Electrosynthesis of enaminones directly from methyl ketones and amines with nitromethane as a carbon source

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

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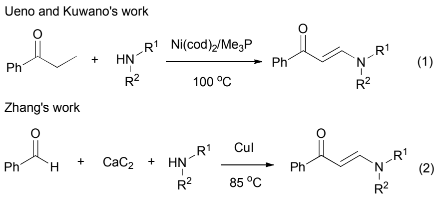
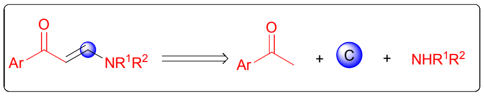
An efficient and mechanistically different method for the electrosynthesis of enaminone directly from methyl ketones, amines and nitromethane was developed. This transition-metal-free method proceeded at room temperature to give a wide array of enaminones in one step, utilizing nitromethane as the carbon source.

Enaminones exist widely in both natural products and synthetic compounds of high utility in pharmaceutical chemistry. [1] The wide synthetic utility along with the synthetic challenge presented by this structural feature have inspired the development of many efficient methods to enable their chemical synthesis.[2-5] However, most of these protocols suffered from the limited availability of starting materials, limited substitution pattern and high reaction temperature. Recently, Ueno, Kuwano and coworkers developed a useful Ni-catalyzed oxidative amination reaction to synthesize enaminone (Scheme 1, eq (1)).[6] More recently, Zhang and coworkers reported an elegant method to construct enaminone catalyzed by CuI with acetylide ion as a synthon (Scheme 1, eq (2)).[7] Although considerable progress has been made in enaminone synthesis, the development of a metal-free strategy to give direct access to various enaminones under mild conditions is highly desired.



Scheme 1. Representative methods for the synthesis of enaminone.

Our laboratory has a longstanding interest in C-H functionalization under electrochemical conditions,[8,9] which motivated us to initiate the study on developing a new electrochemical route toward the synthesis of enaminone. Retrosynthetic analysis showed that construction of enaminone units directly from methyl ketones, amines, and suitable carbon sources would be more appreciable, since it eliminates prefunctionalization steps required for substrate activation (Scheme 2). Herein, we report an efficient and mechanistically different method to synthesize enaminones directly from readily available materials through a convient electrochemical process.



Scheme 2. Retrosynthetic analysis of enaminone.

Initial optimization attempts focused on the survey of suitable carbon source under electrochemical conditions (see Table S1 in the Supporting Information for details). When nitromethane was employed as the carbon source, the corresponding enaminone **3aa** was obtained in 41% yield; while other carbon sources failed to deliver meaningful yields of the product under the same reaction conditions. These results encouraged us to investigate the reaction conditions further (Table 1). Initial experiments were performed to investigate the solvent effect of the reaction. The best yield was obtained by using MeOH as the solvent; however, no products were formed when other commonly used solvents were employed (entries 3-7). Further studies showed that KI was the best electrolyte (entry 8) and iodide ion was essential for the transformation (entries 8, 9 *vs* 10-12). To further improve the yield, some additives were tested. When 2, 2, 2-Trifluoroethanol (TFE) was employed as the additive, the yield increased to 69% (entry 13); when water (5 equiv) was added to the reaction, the yield decreased to 58% (entry 14). Increasing the current to 40 mA led to the decrease of the chemical yield (entry 15). Further assessment of the reaction conditions indicated that an oxygen atmosphere had a positive effect on the reaction; however, a nitrogen atmosphere led to a lower yield (entry 16).

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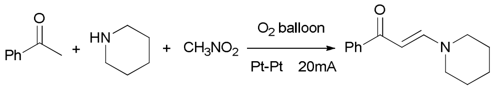
† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

Table 1. Optimization of the reaction conditions.[a]



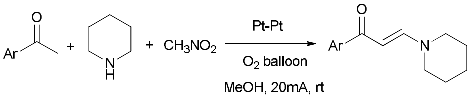
1a **2a** **3aa**

Entry[a]	Solvent	Electrolyte	Yield[b]
1	EtOH	n-Bu_4NI	41
2	MeOH	n-Bu_4NI	55
3	DMSO	n-Bu_4NI	0
4	CH_2Cl_2	n-Bu_4NI	0
5	CH_3CN	n-Bu_4NI	0
6	DMF	n-Bu_4NI	0
7	$MeNO_2$	n-Bu_4NI	0
8	MeOH	KI	63
9	MeOH	NaI	59
10	MeOH	n-Bu_4NBr	trace
11	MeOH	$LiClO_4$	0
12	MeOH	NaBr	trace
13[c]	MeOH	KI	69
14[d]	MeOH	KI	58
15[c,e]	MeOH	KI	53
16[c,f]	MeOH	KI	37

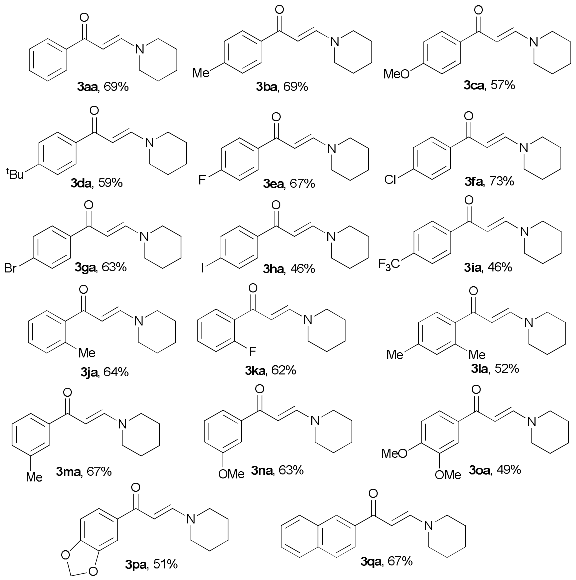
[a] Reaction condition: **1a** (0.5 mmol), **2a** (2 mmol), electrolyte (1 mmol), solvent (8 mL), CH_3NO_2 (1 mL), platinum sheet as an anode and a cathode in an undivided cell, at a constant current of 20 mA for 7 hours, room temperature. [b] Isolated yield. [c] Added 2 equiv of CF_3CH_2OH. [d] Added 5 equiv of H_2O. [e] The current was 40 mA. [f] N_2 was used instead of O_2.

With the optimized conditions in hand, the substrate scope of the reaction was investigated by evaluating a variety of aromatic methyl ketones. As shown in Table 2, the reaction proceeded smoothly with different substrates to afford enaminones in moderate to good yields. The electronic properties of aromatic methyl ketones were found to greatly influence the reaction. In general, the weak electron-donating (Me, **3ba**) and electron-withdrawing (F, Cl, Br, **3ea**-**3ga**) groups has little effect on the yield; however, the strong electron-donating (OMe, **3ca**, **3na**) and moderate electron-withdrawing (CF_3, **3ia**) groups led to the decrease of the chemical yields. For nitro-substituted acetophenone, the reaction didn't proceed at all. On the other hand, the steric effect of substituent on the phenyl group had some influence on the reaction. The *para*- and *meta*-substituents had little effect on the yield, however, *ortho*-substituents led to slightly lower yields (**3ja** *vs* **3ba**, **3ka** *vs* **3ea**).

Table 2. Substrate scope of methyl ketones.[a]



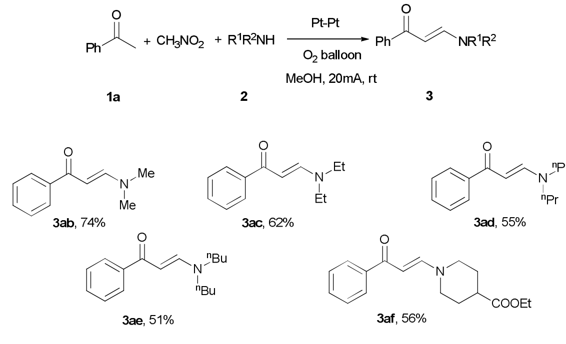
1 **2a** **3**



[a] Reaction condition: **1** (0.5 mmol), **2a** (2 mmol), KI (1 mmol), CF_3CH_2OH (1 mmol), MeOH (8 mL), CH_3NO_2 (1 mL), platinum sheet as an anode and a cathode in an undivided cell, at a constant current of 20 mA for 7 hours, room temperature.

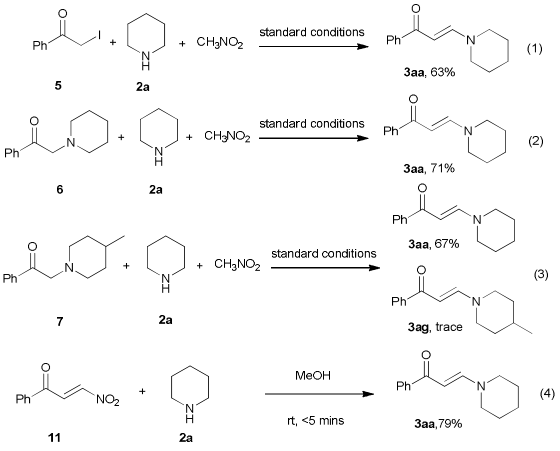
To further establish the general utility of this transformation, the substrate scope for other amines were then examined. As presented in Table 3, a series of aliphatic amines were good reaction partners with acetophenone and nitromethane, and the corresponding enaminones **3ab**-**3af** were obtained in moderate to good yields. For the linear amines, the bulky amine led to a decrease of the yield due to the steric effect (**3ad**-**3ae** *vs* **3ab**-**3ac**). For the cyclic amine with a functional group, the reaction also went smoothly to give the corresponding product **3af** in 56% yield. Importantly, the challenging substrate dimethyl amine (33wt% in water) worked effectively in this reaction system to deliver the product **3ab** in 74 % yield.

Table 3. Substrate scope of amines.[a]



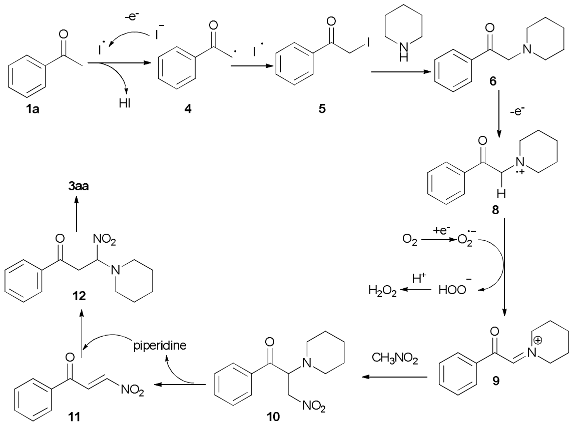
[a] Reaction condition: **1a** (0.5 mmol), **2** (2 mmol), KI (1 mmol), CF_3CH_2OH (1 mmol), MeOH (8 mL), CH_3NO_2 (1 mL), platinum sheet as an anode and a cathode in an undivided cell, at a constant current of 20 mA for 7 hours, room temperature.

To gain insight into the reaction mechanism, a series of control experiments were performed (Scheme 3). When phenacyl iodine **5** was employed as the coupling partner with piperidine **2a** and nitromethane under the standard conditions, the corresponding enaminone **3aa** was obtained in 63% yield, which suggested that phenacyl iodine **5** was likely to be the intermediate of this reaction [Eq. (1)]. As phenacyl iodine **5** was a possible intermediate of this reaction, tertiary amine **6** could be formed easily in the presence of excess amine **2a**. When tertiary amine **6** was employed as the starting material, enaminone **3aa** was obtained in 71% yield, which indicated that tertiary amine **6** was likely to be the intermediate of this tandem reaction [Eq. (2)]. When another tertiary amine **7** was employed as the starting material, enaminone **3aa** was found to be the main product; however, only trace amount of enaminone **3ag** was detected by GC-MS [Eq. (3)]. This result indicated that the tertiary amine may undergo a subsequent C-N cleavage step to lead the final product formation. When nitroalkene **11** was treated with piperidine in MeOH at room temperature, enaminone **3aa** was obtained in 79% yield in less than 5 minutes, which revealed that this tandem reaction may proceed via an addition/elimination sequence involving nitroalkene **11** as an intermediate [Eq. (4)].



Scheme 3. Control experiments.

On the basis of the control experiments and previous studies, a plausible mechanism for this reaction was described in Scheme 4. Initially, phenacyl radical **4**[10] is generated from acetophenone **1a** with the participation of iodide radical[11], accompanied by the liberation of one molecule of HI. Radical coupling[12] between **4** and iodide radical yields phenacyl iodine **5**. Subsequent nucleophilic attack of phenacyl iodine **5** with piperidine provides tertiary amine **6**, which undergoes anodic oxidation to yield intermediate **8**. At the same time, superoxide anion radical $O_2^{\bullet-}$ is generated by electrochemical reduction of O_2.[13] Then proton and electron transfer from **8** to $O_2^{\bullet-}$ yields iminium ion **9**.[14] An addition of nitromethane to **9** leads to the formation of adduct **10**, which is followed by an elimination step to give nitroalkene **11**. Finally, 1, 4-addition of piperidine to nitroalkene **11** affords intermediate **12**, which subsequently undergoes a *β*-H elimination to generate the final product **3aa** with complete *E*-selectivity. [15]



Scheme 4. A plausible mechanism for this reaction.

In summary, we developed an efficient electrochemical method for the synthesis of enaminone directly from readily available starting materials at room temperature. This method not only provided a metal-free route for the synthesis of enaminones but also represented a new strategy for using nitromethane as a capable carbon source. We are currently investigating extensions of this chemistry to other reactions as well as the mechanism responsible for the observed chemistry.

Acknowledgements

Financial support from the Natural Science Foundation of China (2127222, 91213303, 21172205, 21432009, J1030412, 21472177) is greatly acknowledged.

Notes and references

1 (a) J. V. Greenhill, Chem. Soc. Rev., 1977, **6**, 277; (b) B. W. Caprathe, J. C. Jaen, L. D. Wise, T. G. Heffner, T. A. Pugsley, L. T. Meltzer and M. Parvez, J. Med. Chem., 1991, **34**, 2736.

2 For preparations based on 1, 3-dicarbonyl compounds, see: (a) J. Y. Liu, G. E. Cao, W. Xu, J. Cao and W. L. Wang, Appl. Organomet. Chem., 2010, **24**, 685; (b) M. K. Samantaray, C. Dash, M. M. Shaikh, K. Pang, R. J. Butcher and P. Ghosh, Inorg. Chem., 2011, **50**, 1840.

3 For preparations based on enolates and imine derivatives, see: (a) T. S. Saleh, M. A. Al-Omar and H. A. Abdel-Aziz, Lett. Org. Chem., 2010, **7**, 483; (b) M. Ghandi and A. H. Jameà Tetrahedron Lett., 2011, **52**, 4005.

4 For preparations based on other starting materials, see: (a) A.-Z. A. Elassar and A. A. El-Chari, Tetrahedron, 2003, **59**, 8463; (b) H. Ge, M. J. Niphakis and G. I. Georg, J. Am. Chem. Soc. 2008, **130**, 3708; (c) R. Bernini, G. Fabrizi, A. Sferrazza and S. Cacchi, Angew. Chem. Int. Ed., 2009, **48**, 8078; (d) J. Lu, X. Cai and S. M. Hecht, Org. Lett., 2010, **12**, 5189; (e) H. Seki and G. I. Georg, J. Am. Chem. Soc., 2010, **132**, 15512; (f) Y. Wang, X. Bi, W. Q. Li, D. Li, Q. Zhang, Q. Liu and B. S. Ondon, Org. Lett., 2011, **13**, 1722; (g) D. Xiang, X. Xin, X. Liu, R. Zhang, J. Yang and D. Dong, Org. Lett., 2012, **14**, 644; (h) J. Bezenšek, U. Groselj, K. Stare, J. Svete and B. Stanovnik, Tetrahedron, 2012, **68**, 516; (i) X. Xu, P. Du, D. Cheng, H. Wang and X. Li, Chem. Commun., 2012, **48**, 1811; (j) X. Yu, L. Wang, X. Feng, M. Bao and Y. Yamamoto, Chem. Commun., 2013, **49**, 2885; (k) T. Miura, Y. Funakoshi, T. Tanaka and M. Murakami, Org. Lett., 2014, **16**, 2760.

5 T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima and M. Murakami, J. Am. Chem. Soc., 2012, **134**, 17440.

6 S. Ueno, R. Shimizu and R. Kuwano, Angew. Chem. Int. Ed., 2009, **48**, 4543.

7 D. Yu, Y. N. Sum, A. C. C. Ean, M. P. Chin and Y. Zhang, Angew. Chem. Int. Ed., 2013, **52**, 5125.

8 (a) L. Zhang, H. Chen, Z. G. Zha and Z. Y. Wang, Chem. Commun., 2012, **48**, 6574; (b) L. Meng, J. Su, Z. G. Zha, L. Zhang, Z. L. Zhang and Z. Y. Wang, Chem. Eur. J., 2013, **19**, 5542; (c) Z. L. Zhang, J. Su, Z. G. Zha and Z. Y. Wang, Chem. Eur. J., 2013, **19**, 17711; (d) Z. L. Zhang, J. Su, Z. G. Zha and Z. Y. Wang, Chem. Commun., 2013, **49**, 8982; (e) J. Q. Ye, Z. L. Zhang, Z. G. Zha and Z. Y. Wang, Chin. Chem. Lett., 2014, **25**, 1112; (f) H. H. Gao, Z. G. Zha, Z. L. Zhang, H. Y. Ma and Z. Y. Wang, Chem. Commun., 2014, **50**, 5034.

9 For selected references on electrosynthesis, see: (a) H. C. Xu and K. D. Moeller, J. Am. Chem. Soc., 2010, **132**, 2839; (b) Y. Ashikari, T. Nokami and J. Yoshida, J. Am. Chem. Soc., 2011, **133**, 11840; (c) A. Kirste, B. Elsler, G. Schnakenburg and S. R. Waldvogel, J. Am. Chem. Soc., 2012, **134**, 3571; (d) E. E. Finney, K. A. Ogawa and A. J. Boydston, J. Am. Chem. Soc., 2012, **134**, 12374; (e) C. C. Zeng, N. T. Zhang, C. M. Lam and R. D. Little, Org. Lett., 2012, **14**, 1314; (f) T. Sawamura, K. Takahashi, S. Inagi and T. Fuchigami, Angew. Chem. Int. Ed., 2012, **51**, 4413; (g) J. M. Huang, X. X. Wang and Y. Dong, Angew. Chem. Int. Ed., 2011, **50**, 924; (h) T. Morofuji, A. Shimizu and J. Yoshida, J. Am. Chem. Soc., 2013, **135**, 5000; (i) B. R. Rosen, E. W. Werner, A. G. O'Brien and P. S. Baran, J. Am. Chem. Soc., 2014, **136**, 5571.

10 For selected examples involving phenacyl radical, see: (a) A. Banerjee and D. E. Falvey, J. Am. Chem. Soc., 1998, **120**, 2965; (b) M. Neumann, S. Fldner, B. Kȍnig and K. Zeitler, Angew. Chem. Int. Ed., 2011, **50**, 951; (c) K. Xu, Y. Fang, Z. C. Yan, Z .G. Zha and Z. Y. Wang, Org. Lett., 2013, **15**, 2148; (d) N. Jayaraj, P. Jagadesan, S. R. Samanta, J. P. Da Silva and V. Ramamurthy, Org. Lett., 2013, **15**, 4374.

11 For recent reports on about iodide-catalysis, see: (a) S. Tang, Y. Wu, W. Q. Liao, R. P. Bai, C. Liu and A. W. Lei, Chem. Commun., 2014, **50**, 4496; (b) D. Liu and A. W. Lei, Chem. Asian J., 2015, **10**, 806.

12 For selected examples on radical coupling, see: (a) S. Suga, S. Suzuki and J. Yoshida, J. Am. Chem. Soc., 2002, **124**, 30; (b) T. J. Anderson, G. D. Jones and D. A. Vicic, J. Am. Chem. Soc., 2004, **126**, 8100; (c) K. Xu, Y. B. Hu, S. Zhang, Z. G. Zha and Z. Y. Wang, Chem. Eur. J., 2012, **18**, 9793; (d) X. Zheng, X. Dai, H. Yuan, C. Ye, J. Ma and P. Q. Huang, Angew. Chem. Int. Ed., 2013, **52**, 3494; (e) L. L. Zhou, S. Tang, X. T. Qi , C. T. Lin, K. Liu, C. Liu, Y. Lan and A. W. Lei, Org. Lett., 2014, **16**, 3404; (f) D. Hager and D. W. C. MacMillan, J. Am. Chem. Soc., 2014, **136**, 16986; (g) D. Liu, Y. Li, X. T. Qi, C. Liu, Y. Lan and A. W. Lei, Org. Lett., 2015, **17**, 998; (h) M. Nagatomo, H. Nishiyama, H. Fujino, M. Inoue, Angew. Chem. Int. Ed., 2015, **54**, 1537.

13 For examples on electrochemical reduction of dioxygen into superoxide anion radical, see: (a) D. T. Sawyer and J. L. Roberts, J. Electroanal. Chem., 1962, **12**, 90; (b) J.-M. Savéant, Chem. Rev., 2008, **108**, 2348; (c) M. Shao, P. Liu and R. R. Adzic, J. Am. Chem. Soc., 2006, **128**, 7408; (d) C. Z. Zhang, F.-R. F. Fan and A. J. Bard, J. Am. Chem. Soc., 2009, **131**, 177.

14 For the application of superoxide anion radical as a base for proton abstraction, see: (a) E. J. Nanni and D. T. Sawyer, J. Am. Chem. Soc., 1980, **102**, 7593; (b) W. T. Monte, M. M. Baizer and R. D. Little, J. Org. Chem., 1983, **48**, 803; (c) A. A. Frimer, T. Farkash-Solomon and G. Aljadeff, J. Org. Chem., 1986, **51**, 2093; (d) Z. W. Liang, S. Xu, W. Y. Tian and R. H. Zhang, Beilstein J. Org. Chem., 2015, **11**, 425.

15 The byproducts of this elimination reaction might be HNO and H_2O. A similar reaction path was demonstrated by: (a) H. Shiraishi, T. Nishitani, S. Sakaguchi and Y. Ishii, J. Org. Chem., 1998, **63**, 6234; (b) S. Maiti, S. Biswas and U. Jana, J. Org. Chem., 2010, **75**, 1674; (c) S. Santra, A. K. Bagdi, A. Majee and A. Hajra, Adv. Synth. Catal., 2013, **355**, 1065.