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Iron-Catalyzed Selective Oxidation of *N*-Methyl Amines: Highly Efficient Synthesis of Methylene-Bridged bis-1,3-Dicarbonyl Compounds

Haijun Li, Zhiheng He, Xingwei Guo, Wenjuan Li, Xuhui Zhao, and Zhiping Li*

Department of Chemistry, Renmin University of China, Beijing 100872, China

zhipingli@ruc.edu.cn

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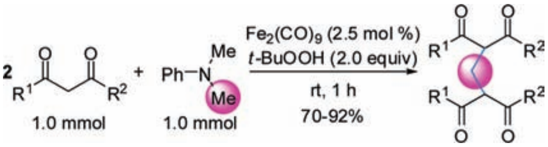
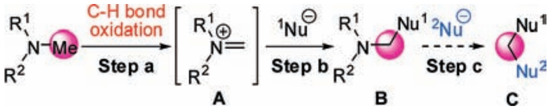
ABSTRACT



Methylene-bridged bis-1,3-dicarbonyl derivatives were synthesized efficiently by iron-catalyzed oxidative reactions of 1,3-dicarbonyl compounds and *N*,*N*-dimethylaniline. Bipyrazoles and substituted 1,4-dihydropyridine were obtained by the reactions of bis-1,3-dicarbonyl compounds with hydrazines and ammonium acetate, respectively.

The oxidation of amines,[1,2] especially *N*-methyl amines,[3] is an important process and has attracted much interest in chemistry and biochemistry. Catalytic functionalization of a C−H bond adjacent to a nitrogen atom presents a direct and efficient method of synthesizing amine derivatives.[4] A general mechanism for the oxidative functionalization of *N*-methyl amine is shown in Scheme 1.[5] An iminium species **A** is generated by selective oxidation C−H bond adjacent to nitrogen (Step a). Subsequently, the nucleophilic addition reaction affords the oxidative Mannich-type products **B** in the presence of a nucleophile (Step b), which were generally synthesized by the Mannich reaction or the aza-Michael addition reaction. However, selective double alkylation of *N*-methyl amines is virtually unknown (Step c).[6]

Scheme 1. Direct Oxidative Functionalization of *N*-Methyl Amines



The application of readily available and nontoxic iron catalysts instead of expensive and sensitive catalysts is highly attractive for chemical synthesis.[7] Iron-catalyzed oxidation of *N*-methyl amines is of considerable interest in synthetic chemistry.[8,9] In conjunction with our recent result on selective oxidation of C−H bonds adjacent to heteroatoms,[10] we herein report a novel and efficient method of synthesizing

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(5) For representative reviews, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Li, C.-J.; Li., Z. *Pure Appl. Chem.* **2006**, *78*, 935. (c) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225. (d) Murahashi, S.-I. *Pure Appl. Chem.* **1992**, *64*, 403.

(6) (a) Murata, S.; Miura, M.; Nomura, M. *J. Org. Chem.* **1989**, *54*, 4700. (b) Murata, S.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1989**, 116.

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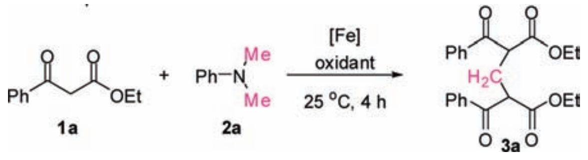
bis-1,3-dicarbonyl derivatives[11] by the iron-catalyzed reactions of 1,3-dicarbonyl compounds with *N*-methyl amines under mild reaction conditions.

Table 1. Optimization of the Reaction Conditions



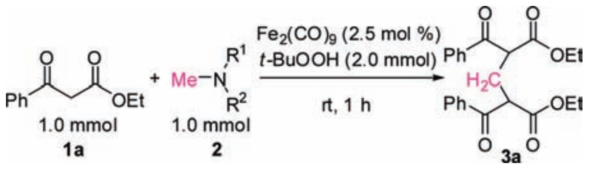
entry	**1a** (mmol)	**2a** (mmol)	[Fe] (%)[a]	oxidant (mmol)[b]	yield (%)[a]
1	0.5	2.0	$FeCl_3$ (10)	(t-BuO)$_2$ (1.5)	5
2	0.5	2.0	$Fe(OAc)_2$ (10)	(t-BuO)$_2$ (1.5)	6
3	0.5	2.0	$FeBr_2$ (10)	(t-BuO)$_2$ (1.5)	27
4	0.5	2.0	$FeCl_2$ (10)	(t-BuO)$_2$ (1.5)	52
5	0.5	2.0	$Fe_2(CO)_9$ (5)	(t-BuO)$_2$ (1.5)	39
6	0.5	2.0	$Fe_2(CO)_9$ (5)	t-BuOOH (1.5)	51
7	1.0	1.0	$Fe_2(CO)_9$ (2.5)	t-BuOOH (2.0)	75
8	1.0	1.0	$Fe_2(CO)_9$ (2.5)	t-BuOOH (2.0)	86[c]

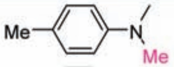
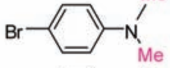
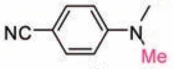
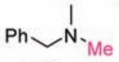
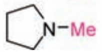
[a] Based on **1a**. [b] *t*-BuOOH (5.5 M in decane). [c] One hour.

The reaction of ethyl 3-oxo-3-phenylpropanoate **1a** and *N*,*N*-dimethyl aniline **2a** was investigated to examine the suitable reaction conditions (Table 1). $FeCl_3$, $Fe(OAc)_2$, and $FeBr_2$ were ineffective catalysts for the formation of **3a** (entries 1−3). The desired product **3a** was obtained in 52% yield when $FeCl_2$ was used as a catalyst (entry 4). Although $Fe_2(CO)_9$ led to 39% yield of **3a** at 25 °C,[12] a 51% yield of **3a** was achieved when *tert*-butyl hydrogenperoxide (TBHP) was used instead of di-*tert*-butyl peroxide (entries 5 and 6). Importantly, up to 75% yield of **3a** was obtained using 2.5 mol % of $Fe_2(CO)_9$ and 2.0 equivalents of TBHP (entry 7). The yield of **3a** was further improved to 86% when the reaction time was one hour (entry 8). Some uncharacterized byproducts were observed with a prolonged reaction time. These results demonstrated that low loading catalyst and short reaction time are essential for the high selectivity of the present transformation.

Other *N*-methyl amines were also investigated under the optimized reaction conditions (Table 2). The reaction of **1a** with 4-methyl *N*,*N*-dimethyl aniline affords a comparable yield of the desired product **3a** (Table 2, entry 1 vs Table 1, entry 8), whereas electron-withdrawing substituted aniline gave **3a** in low yields (entries 2 and 3). These results were consisted with the oxidative activities of 4-X-*N*,*N*-dimethylanilines.[13] Notably, aliphatic tertiary amines were not effective methylenic sources (entries 4 and 5).

Table 2. Reactions of **1a** with Other *N*-Methyl Amines



entry	2	isolated yield (%)
1		85
2		61
3		14
4		54
5		25

Subsequently, the scope of the present transformation was examined using *N*,*N*-dimethyl aniline **2a** as a methylenic unit source. Various 1,3-dicarbonyl compounds were transformed into the corresponding methylene-bridged bis-1,3-dicarbonyl products **3a** with good to excellent yields under the optimized conditions (Scheme 2). Not only β-ketone esters but also β-ketone amide and 1,3-diketones reacted smoothly with *N*,*N*-dimethyl aniline **2a**. No obvious electronic effect was observed with **1** bearing an aromatic ring. However, the desired methylene-bridged bis-1,3-dicarbonyl products were obtained in low yields (ca.10−30%) when pentane-2,4-dione and ethyl 3-oxobutanoate were used. We postulated that a stabilized intermediates introduced by aromatic substituent improves the efficiency of the present transformation.[14] Two diastereomers were obtained in ratios between 0.7 and 1.[15]

Pyrazoles are an important class of heteroaromatic ring systems and exist in nature products, medical molecules, and metallic ligands.[16] With the methylene-bridged bis-1,3-

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(7) For representative reviews, see: (a) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (b) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (c) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (d) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (e) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(8) Iron-catalyzed oxidation of *N*-methyl amines, see: Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701.

(9) Other metal-catalyzed reactions, see: [Ru]: (a) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (b) Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931. (c) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312[Cu]: (d) Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2009**, *11*, 3730. (e) Chu, L.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 2197. (f) Xu, X.; Li, X. *Org. Lett.* **2009**, *11*, 1027. (g) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953. (h) Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (i) Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007**, *9*, 3813. (j) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810[Rh]: (k) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

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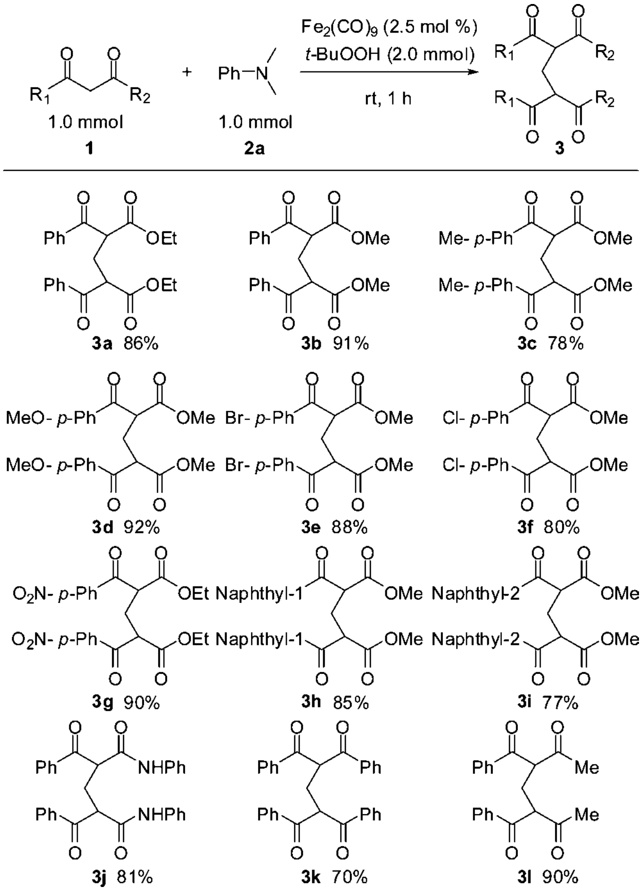
(12) The oxidative coupling product **9** was obtained as the major product in 53% yield and bis-1,3-dicarbonyl compound **4a** was only isolated in trace amount at 80 °C; see ref 10.

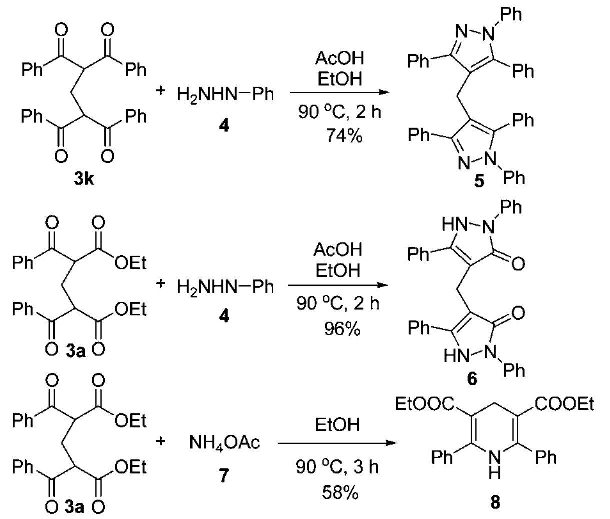
(13) (a) References 8 and 9. (b) Baciocchi, E.; Lanzalunga, O.; Lapi, A.; Manduchi, L. *J. Am. Chem. Soc.* **1998**, *120*, 5783.

Scheme 2. Some Representative Results

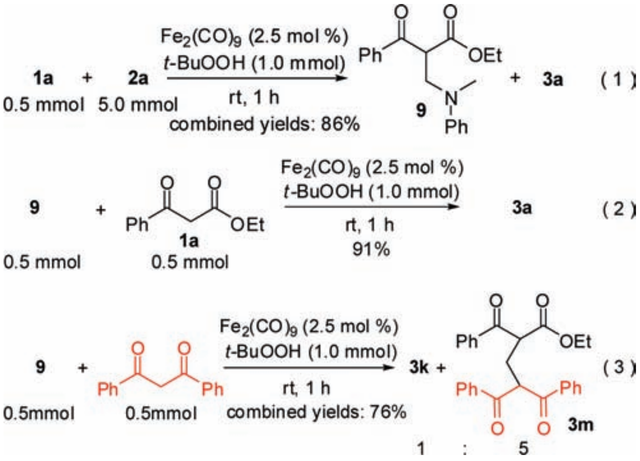


dicarbonyl compounds in hands, bipyrazoles were synthesized efficiently by the reported method (Scheme 3).[17] In addition, the substituted 1,4-dihydropyridine **8** was obtained in moderate yield by the reaction of **3a** and ammonium acetate **7**. The applications of the bis-1,3-dicarbonyl compounds **1** and their derivatives in coordination chemistry and synthetic chemistry are under investigated in this lab.

Scheme 3. Representative Drivatization of **3**

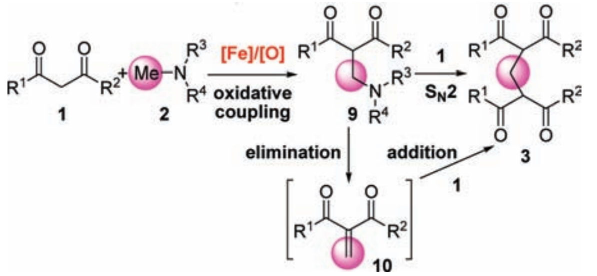


Interestingly, the oxidative coupling product **9** was obtained in 47% yield together with 37% yield of **3a** in the presence of 10 equiv of **2a** (eq 1). Subsequently, **9** was subjected to the standard reaction conditions and **3a** was obtained with 91% yield (eq 2). The results suggested that the oxidative-coupling product **9** is most likely a possible intermediate for the present transformation. It was further confirmed by the formation of the crossed product **3m** under the standard reaction conditions (eq 3).



Based on these results, a plausible scenario of the formation of the methylene-bridged bis-1,3-dicarbonyl product **3** is illustrated in Scheme 4. The reaction of **1** and **2** affords the oxidative coupling product **9**. **3** is formed by either nucleophilic substitution reaction or the tandem reaction of Cope elimination and Michael addition via a intermediate **10** in the presence of iron catalyst and oxidant. However, the reaction of 1,3-dicarbonyl compounds **1** with formaldehyde, which was generated *in situ* via iron-catalyzed

Scheme 4. Possible Pathways for the Formation of **3**



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(14) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505.

(15) The ratios of diastereomers were given in the Supporting Information.

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oxidative *N*-demethylation,[18] would also afford the methylene-bridged bis-1,3-dicarbonyl product **3**.[19] Therefore, this alternative pathway could not be fully excluded at this stage.

In summary, we demonstrated a novel and efficient method of synthesizing methylene-bridged bis-1,3-dicarbonyl derivatives via iron-catalyzed oxidation of *N*-methyl amines. Bipyrazoles and substituted 1,4-dihydropyridine were obtained by the reaction of methylene-bridged bis-1,3-dicarbonyl compounds with hydrazines and ammonium acetate. The mild reaction conditions and the high efficiency of the oxidative functionalization make the present transformation attractive for future applications.

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Supporting Information Available: Representative experimental procedure, characterization of all new compounds, Nash test and ^{1}H NMR and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The formation of formaldehyde in the present transformation was proven by Nash test; the detailed experiments of Nash test were given in the Supporting Information.

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