ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 11333–11335

www.rsc.org/chemcomm

COMMUNICATION

TBAI-catalyzed oxidative coupling of aminopyridines with β-keto esters and 1,3-diones—synthesis of imidazo[1,2-*a*]pyridines†

Lijuan Ma, Xianpei Wang, Wei Yu* and Bing Han*

Received 16th June 2011, Accepted 17th August 2011
DOI: 10.1039/c1cc13568f

TBAI could catalyze the direct oxidative C–N coupling of 2-aminopyridines with β-keto esters and 1,3-diones, which affords imidazo[1,2-*a*]pyridines as the products. The reaction was realized under metal-free conditions by using *tert*-butyl hydroperoxide (TBHP) as the oxidant.

The imidazo[1,2-*a*]pyridine ring system constitutes the core structure of many pharmacologically important compounds. Several synthetic strategies have been developed to gain access to the variously substituted imidazo[1,2-*a*]pyridine rings.[1,2] The coupling reaction of 2-aminopyridines with α-halocarbonyl compounds provides a practical method which has found wide applications in medicinal chemistry and drug synthesis.[3] Very recently, we developed a new protocol for the synthesis of imidazo[1,2-*a*]pyridine rings which employs the PIDA-mediated oxidative coupling of 2-aminopyridines with β-keto esters or 1,3-diones.[4] This method is advantageous in terms of high efficiency and easy operation, and obviates the pre-functionalization of the 1,3-dicarbonyl compounds.

From both environmental and economical points of view, it is highly desirable to develop oxidizing systems where only a catalytic amount of hypervalent iodine reagent is required. The hypervalent iodine reagent can be generated *in situ* and recycled by using another cheap and nontoxic terminal oxidant.[5] So far the most investigated catalytic system based on this notion involves the use of ArI as the catalyst and *m*CPBA or urea–H_2O_2 as the stoichiometric oxidant. Other systems are much less explored. Recently, Ishihara *et al.* revealed the synthetic potential of a novel oxidizing system which features the use of quaternary ammonium iodide as the catalyst and 30% H_2O_2 or *tert*-butyl hydroperoxide (TBHP) as the stoichiometric oxidant.[6] This system was first employed by Kirihara *et al.* to realize the oxidative homocoupling of thiols to disulfides.[7] The studies by Ishihara *et al.* showed that quaternary ammonium iodides could efficiently catalyze the α-oxy functionalization of carbonyl compounds, and by using the chiral quaternary ammonium iodides, the enantioselective intramolecular oxidative C–O coupling was realized. The reaction was proposed to be effected by the quaternary ammonium (hypo)iodite salts generated *in situ* from the oxidation of quaternary ammonium iodides by TBHP or H_2O_2. In another study, Wan *et al.* employed the reagent combination of tetrabutyl ammonium iodide (TBAI) and TBHP to realize the intermolecular C–O coupling of carboxylic acids and ethers.[8] Encouraged by these results, we envisioned that this methodology might also be applied to the intra- and intermolecular oxidative C–N coupling.[9] As a preliminary study toward this end, we found that imidazo[1,2-*a*]pyridines could be prepared from 2-aminopyridines with β-keto esters and 1,3-diones *via* the TBAI-catalyzed oxidative coupling.

We commenced our study by subjecting compounds 2-aminopyridine **1a** and ethyl 2-benzoylacetate **2a** to 2.0 equiv. of 30% H_2O_2 or TBHP (70% in water) in the presence of 0.1 equiv. of TBAI under various conditions. Our previous work demonstrates that a catalyic amount of $BF_3{\cdot}Et_2O$ can catalyze the $PhI(OAc)_2$-mediated coupling reaction between 2-aminopyridines and 1,3-dicarbonyl compounds.[4] Therefore, $BF_3{\cdot}Et_2O$ was used here too to promote the reaction (eqn (1)). Initial attempt showed that the reaction did not take place at room temperature. So the reaction was performed at elevated

Table 1 Screening of the conditions for the TBAI-catalyzed reaction between **1a** and **2a**[a]

Entry	**1a**/**2a**	Equiv. of TBAI	Oxidant (2 equiv.)	Equiv. of $BF_3{\cdot}Et_2O$	Reaction time/h	Yield of **3a**[b] (%)
1	1 : 1	0.1	30% H_2O_2	0.2	16	47
2	1 : 1	0.1	TBHP	0.2	16	53
3	1 : 1	None	TBHP	0.2	16	0
4	1 : 1.5	0.1	TBHP	0.2	12	30
5	1.2 : 1	0.1	TBHP	0.2	23	71
6	**1.5 : 1**	**0.1**	**TBHP**	**0.2**	**12**	**81**
7	1.5 : 1	0.05	TBHP	0.2	35	76
8	1.5 : 1	0.1	TBHP	None	12	48
9	1.5 : 1	0.1	TBHP	1.0	12	44
10	1.5 : 1	1.0	TBHP	0.2	16	10
11	1.5 : 1	0.1	30% H_2O_2	0.2	35	64

[a] The reaction was performed at 80 °C with 2.0 mmol of 30% H_2O_2 or TBHP (70% in water) as the oxidant. 5 mL CH_3CN was used as the solvent unless otherwise indicated. [b] Isolated yield based on the compound used in fewer amount.

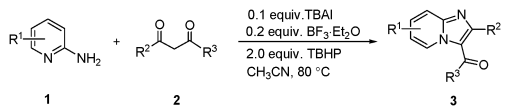
State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, P. R. China. E-mail: yuwei@lzu.edu.cn, hanb@lzu.edu.cn; Fax: +86-931-8912582; Tel: +86-931-8912500

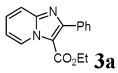
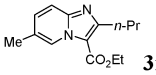
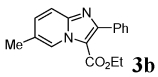
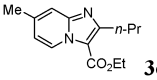
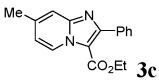
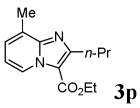
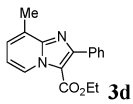
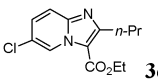
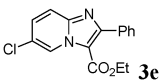
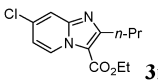
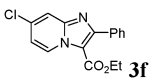
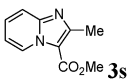
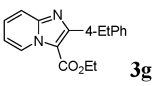
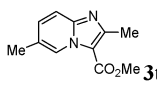
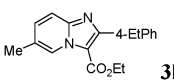
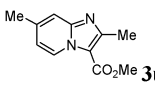
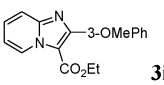
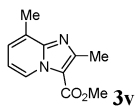
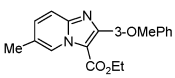
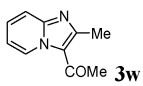
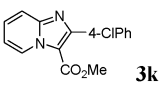
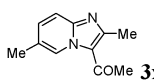
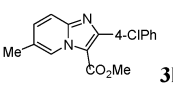
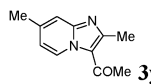
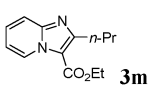
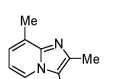
† Electronic supplementary information (ESI) available: General experimental procedures, detailed information on the optimization of reaction conditions, control experiments, characterization data, ^1H NMR and ^{13}C NMR spectra of compounds **3a–3z**. CCDC 824738. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc13568f

temperatures next. We found that the expected reaction took place at 80 °C, and when CH_3CN was used as the solvent, **3a** was obtained in yields of 47% and 53%, respectively, with 30% H_2O_2 and TBHP as the oxidants (Table 1, entries 1 and 2). The yield was improved by raising the amount of **1a** (Table 1, entries 5, 6 and 11). On the other hand, adjusting the ratio of **1a** and **2a** to 1 : 1.5 led to inferior results (Table 1, entry 4). Besides CH_3CN, several other solvents were also used, but the results were less satisfactory.[10]

(1)

Table 2 Synthesis of imidazo[1,2-*a*]pyridines **3** *via* the TBAI-catalyzed reactions between **1** and **2**[a]



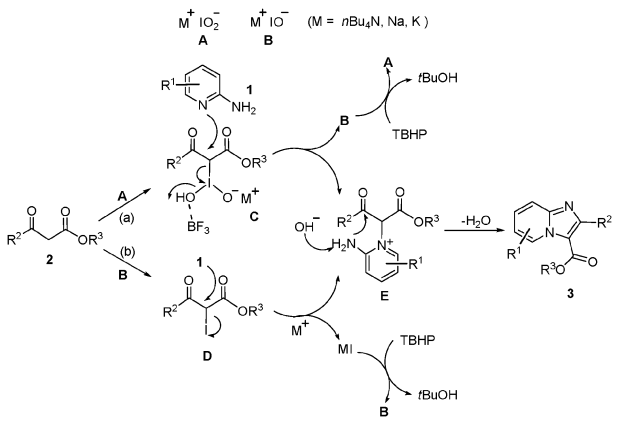
Entry	Reaction time/h	Product	Yield[b] (%)	Entry	Reaction time/h	Product	Yield[b] (%)
1	12	 **3a**	81	14	11	 **3n**	57
2	12	 **3b**	82	15	11	 **3o**	52
3	10	 **3c**	83	16	24	 **3p**	45
4	16	 **3d**	82	17	48	 **3q**	21
5	36	 **3e**	23	18	48	 **3r**	18
6	36	 **3f**	37	19	9	 **3s**	65
7	12	 **3g**	66	20	11	 **3t**	55
8	10	 **3h**	70	21	11	 **3u**	54
9	14	 **3i**	65	22	9	 **3v**	54
10	11	 **3j**	78	23	10	 **3w**	63
11	11	 **3k**	68	24	12	 **3x**	45[c]
12	17	 **3l**	73	25	12	 **3y**	39[c]
13	24	 **3m**	58	26	10	 **3z**	61

[a] The reaction was performed with 1.5 mmol of **1** and 1.0 mmol of **2** unless otherwise specified. [b] Isolated yield based on **2**. [c] 1.0 mmol of **1** and 1.1 mmol of **2** were used for the convenience of product purification and the yield was based on **1**.

Control experiments showed that TBAI played the key role in the reaction (Table 1, entry 3). It is noteworthy that while using a catalytic amount of TBAI ensures a good result, too much TBAI has negative effect on the reaction (Table 1, entry 10). The reaction also took place in the absence of $BF_3{\cdot}Et_2O$, but the yield of **3a** was lower (Table 1, entry 8). On the other hand, using 1.0 equiv. of $BF_3{\cdot}Et_2O$ was less favorable for the reaction, consistent with our previous findings (Table 1, entry 9).[4] Besides TBAI, NaI and KI were also capable of catalyzing the reaction, indicating that an ammonium counterion was not necessary during the reaction.[10]

To examine the scope of this protocol, the optimized conditions (Table 1, entry 6) were then applied to the synthesis of a variety of substituted imidazo[1,2-*a*]pyridines **3** from 2-aminopyridines **1** and 1,3-dicarbonyl compounds **2**.‡ The results are listed in Table 2. 2-Phenyl-imidazo[1,2-*a*]pyridine-3-carboxylates were prepared in good yields except for the chloro-substituted **3e** and **3f**, in which cases the reaction was not complete even after prolonged reaction time (Table 2, entries 5–6). The structure of **3d** was confirmed by X-ray crystallographic analysis.[11] The reaction can also be used to prepare 2-alkyl substituted imidazo[1,2-*a*]pyridine-3-carboxylates (**3m–3v**), and 2-alkyl-3-acyl imidazo[1,2-*a*]pyridines (**3w–3z**). Compounds **3** are useful intermediates for the synthesis of pharmaceutically important compounds.[12]

To account for the reaction process described above, a mechanism (Scheme 1, path a) was proposed based on Ishihara's study[6] and our experiments. In this mechanism, MI is firstly oxidized by TBHP to $M^+[IO_2]^-$ (**A**), and the latter reacts with **2** to give intermediate **C**. Nucleophilic attack of **C** by **1** affords **E**, from which product **3** is generated. The released $M^+[IO]^-$ (**B**) is reoxidized to **A** by TBHP. Catalytic amount of $BF_3{\cdot}Et_2O$ has beneficial effect on the reaction, probably because it can enhance the electrophilicity of **A** as well as facilitate the removal of **B** from **C**. On the other hand, using 1 equiv. $BF_3{\cdot}Et_2O$ hampers the function of **1** as the nucleophile, thus resulting in lowering of the yield.[4] It is also possible that the active oxidant was **B**, which reacted with **2** to generate **D** (Scheme 1, path b). However, control experiments showed that the reaction of **1a** with ethyl 2-iodo-3-oxo-3-phenylpropanoate only affords **3a** in low yield. Besides, we failed to obtain **D** when **2a** was treated with TBAI and TBHP in the presence of $BF_3{\cdot}Et_2O$. Therefore, path b seems less likely the working mechanism. Another alternative mechanism, which involves firstly the condensation between **1** and **2**, and then the oxidation of thus formed enamine ester, is not possible as the condensation of **1a** and **2a** cannot take place in refluxing acetonitrile.[10]



Scheme 1

In summary, this work demonstrates that the direct oxidative C–N coupling between 2-aminopyridines and β-keto esters or 1,3-diones can be effected by using TBAI as the catalyst and TBHP as the terminal oxidant. The reaction constitutes a simple and economical protocol for the synthesis of imidazo[1,2-*a*]pyridines.

The authors thank the National Natural Science Foundation of China (No. 20772053) for financial support.

Notes and references

‡ General procedure for the synthesis of substituted imidazo-[1,2-*a*]pyridines (**3**) from 2-aminopyridines (**1**) and β-keto esters and acetylacetone (**2**): a mixture of 1.0 mmol of **2**, 1.5 mmol of **1**, 0.1 mmol of TBAI, 2.0 mmol of TBHP (70% in water) and 26 μL of $BF_3{\cdot}Et_2O$ (0.2 mmol) in 5 mL of CH_3CN was stirred in a 15 mL Pyrex screw-cap pressure tube at 80 °C for the indicated period of time shown in Table 2. After the reaction finished as indicated by TLC, the reaction mixture was cooled to room temperature, and then poured into 15 mL saturated Na_2SO_3 solution. The product was extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the residue was treated with silica gel chromatography to give product **3**.

1 A. R. Katritzky, Y.-J. Xu and H. Tu, *J. Org. Chem.*, 2003, **68**, 4935, and cited references therein.
2 N. Chernyak and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2010, **49**, 2743, and cited references therein.
3 For recent examples, see: (*a*) G. Trapani, V. Laquintana, N. Denora, A. Trapani, A. Lopedota, A. Latrofa, M. Franco, M. Serra, M. G. Pisu, I. Floris, E. Sanna, G. Biggio and G. Liso, *J. Med. Chem.*, 2005, **48**, 292; (*b*) V. Laquintana, N. Denora, A. Lopedota, H. Suzuki, M. Sawada, M. Serra, G. Biggio, A. Latrofa, G. Trapani and G. Liso, *Bioconjugate Chem.*, 2007, **18**, 1397; (*c*) N. Denora, V. Laquintana, M. G. Pisu, R. Dore, L. Murru, A. Latrofa, G. Trapani and E. Sanna, *J. Med. Chem.*, 2008, **51**, 6876; (*d*) H. Kishino, M. Moriya, S. Sakuraba, T. Sakamoto, H. Takahashi, T. Suzuki, R. Moriya, M. Ito, H. Iwaasa, N. Takenaga, A. Ishihara, A. Kanatani, N. Sato and T. Fukami, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4589.
4 X. Wang, L. Ma and W. Yu, *Synthesis*, 2011, 2445.
5 (*a*) R. D. Richardson and T. Wirth, *Angew. Chem., Int. Ed.*, 2006, **45**, 4402; (*b*) M. Ochiai and K. Miyamoto, *Eur. J. Org. Chem.*, 2008, 4229; (*c*) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073; (*d*) T. Dohi, *Chem. Pharm. Bull.*, 2010, **58**, 135.
6 (*a*) M. Uyanik, H. Okamoto, T. Yasui and K. Ishihara, *Science*, 2010, **328**, 1376; (*b*) M. Uyanik and K. Ishihara, *Chim. Oggi.*, 2011, **29**, 18; (*c*) M. Uyanik, D. Suzuki, T. Yasui and K. Ishihara, *Angew. Chem., Int. Ed.*, 2011, **50**, 5331.
7 M. Kirihara, Y. Asai, S. Ogawa, T. Noguchi, A. Hatano and Y. Hirai, *Synthesis*, 2007, 3286.
8 L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu and X. Wan, *Chem.–Eur. J.*, 2011, **17**, 4085. However, in this work, a free radical mechanism was proposed by the authors to rationalize the observations.
9 After submission of this paper, a work dealing with TBAI-catalyzed C–N oxidative coupling with TBHP as the oxidant was published. See: T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner and B. J. Nachtsheim, *Org. Lett.*, 2011, **13**, 3754.
10 Please see ESI† for more details.
11 CCDC 824738.
12 (*a*) P. George and C. Giron, *Patent Application US 4,650,796*, 1987; (*b*) G. Trapani, M. Franco, L. Ricciardi, A. Latrofa, G. Genchi, E. Sanna, F. Tuveri, E. Cagetti, G. Biggio and G. Liso, *J. Med. Chem.*, 1997, **40**, 3109.