ChemComm

COMMUNICATION



View Article Online View Journal | View Issue

Fe-Catalysed oxidative C–H/N–H coupling between aldehydes and simple amides[†]

Jing Wang,^a Chao Liu,^a Jiwen Yuan^a and Aiwen Lei*^{ab}

Cite this: Chem. Commun., 2014, 50, 4736 Received 25th February 2014,

Accepted 19th March 2014 DOI: 10.1039/c4cc01447b

www.rsc.org/chemcomm

A novel oxidative coupling of aldehydes with simple amides, most likely involving a radical process, was achieved through the use of an iron catalyst. Various amides were utilized as substrates to easily construct imides by coupling with aldehydes. A catalytic cycle involving the benzoyl halide intermediate is proposed based on our experimental results.

The oxidative coupling between R¹H and R²H,¹ which avoids the use of organo halides (or halide equivalents) and organometallic reagents, possesses practical advantages for applications and has attracted much attention in recent years. Many advancements have been made in this emerging field, in which main efforts have been put on the oxidative cross coupling between two C–H bonds for the construction of C–C bonds. In comparison, the direct oxidative coupling between C–H and N–H for the construction of C–N bonds has been less reported.² The mainly utilized NH nucleophiles were amines³ and special amides (such as picolinamide⁴ or primary amides⁵). However, to the best of our knowledge, no reports have been demonstrated by using simple chainlike secondary amides as the nucleophiles to oxidatively couple with aldehydes for the construction of imides.⁶

Imides⁷ are present in biologically active molecules and have been targets of interest for the synthesis of pharmaceuticals⁸ such as variotin, aniracetam, and several heterocycles,⁹ which are present in abundance in biologically active natural products. As we know, the use of acyl halides as acylation reagents is a common strategy to construct imides,^{7a} whereas the method is problematic due to the unstable and corrosive properties of the corresponding acyl halides. Comparatively, an aldehyde would be the elegant acylation reagent, due to its wide availability and no release of halide waste. Herein, we report a Fe-catalysed oxidative coupling approach for the construction of imides *via* acylation of simple amides with aldehydes as the acylation reagents (eqn (1)).



Recently, we initiated a program toward the aldehyde C-H activation for preparing various carbonyl compounds.¹⁰ During the course of our research, we were pleased to discover that an aldehyde could be converted to the corresponding acyl chloride in the presence of $FeCl_2$ and TBHP (eqn (2)). Due to the unstable property of the corresponding acyl chloride, the stoichiometric reaction was detected by in situ IR.¹¹ The kinetic profile of the reaction clearly revealed a new component A which increased in intensity as the reaction proceeded (Fig. 1(A)); this new component was assigned to be benzoyl chloride by comparison with an authentic sample (Fig. 1(B)). This indicated that acyl chloride could be prepared in situ with aldehydes and FeCl₂ in the presence of TBHP. We envisioned that this acyl chloride generation from aldehyde could be utilized in the direct synthesis of imides from aldehydes and amides. Consequently, FeCl2 combined with TBHP was initially applied to test the oxidative coupling of aldehydes with amides to construct imides.

$$\begin{array}{r} PhCHO + FeCl_{2} \\ 5 \\ \vdots \\ 1 \end{array} \xrightarrow{3 \text{ equiv IBHP}} PhCOCI \qquad (2)$$



Fig. 1 (A) Kinetic profile of the reaction. (B) IR spectra of component A (blue curve) and the authentic sample of benzoyl chloride (red curve).

^a College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei 430072, P. R. China. E-mail: aiwenlei@whu.edu.cn;

Fax: +86-27-68754067; Tel: +86-27-68754672

^b National Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang, Jiangxi 330022, P. R. China

[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc01447b

ChemComm

Table 1 Impact of reaction parameters on Fe-catalysed oxidative coupling of N-benzylacetamide with benzaldehyde^a

	NH + ∃n − 2	[M], C Ph Solvent	Dxidant , 60 °C,16 h	O O N Ph Bn
Entry		Oxidant	Solvent	Yield ^b (%)
1	FeCl ₂	TBHP	DCE	28
2	FeBr ₂	TBHP	DCE	80
3	$Fe(OAc)_2$	TBHP	DCE	n.d.
4	$Fe(OTf)_2$	TBHP	DCE	Trace
5	None	TBHP	DCE	n.d.
6	FeBr ₂	TBHP	Benzene	Trace
7	FeBr ₂	TBHP	Toluene	24
8	FeBr ₂	TBHP	CH_3CN	31
9	FeBr ₂	DTBP	DCE	Trace
10	FeBr ₂	AIBN	DCE	n.d.
11	FeBr ₂	BPO	DCE	Trace

n.d. = no desired product. TBHP = tert-butyl hydroperoxide, DTBP = 2-(tert-butylperoxy)-2-methylpropane, BPO = benzoic peroxyanhydride, AIBN = azobisisobutyronitrile. a Unless otherwise noted, the reaction was carried out with 1a (0.5 mmol), 2a (1.5 mmol), oxidant (1.0 mmol), catalyst (0.025 mmol), solvent (2.0 mL), 60 °C, 16 h, Ar. b The yield was determined by GC analysis with dibenzo [b,d] furan as the internal standard.

We started our investigation by utilizing the reaction of N-benzylacetamide 1a with benzaldehyde 2a as a model reaction to test different reaction conditions. Selected data are listed in Table 1. To our delight, as expected, a 28% GC yield of the desired product 3aa was obtained by using 5 mol% FeCl₂ as the catalyst (Table 1, entry 1), indicating that a catalytic cycle was operating under current conditions. Considering that acyl bromide is more active than acyl chloride, FeBr₂ was further tested. Indeed, the yield of 3aa showed a remarkable improvement and an 80% yield of 3aa was obtained (Table 1, entry 2). When FeBr₂ was replaced by nonhalide containing iron salts such as Fe(OAc)₂ or Fe(OTf)₂, none or a trace amount of desired product was obtained (Table 1, entries 3 and 4), indicating that Fe catalyst precursors containing halogens were crucial for the coupling process. Without catalysts, no desired product was obtained (Table 1, entry 5). Solvent screening showed that the desired product could be obtained in benzene or toluene, but only in low yields which may result from the poor solubility of FeBr₂ in these solvents (Table 1, entries 6 and 7). A 31% GC yield of the desired product 3aa was obtained in coordinating solvent CH3CN (Table 1, entry 8). TBHP gave excellent yield for this oxidative coupling reaction. However, other oxidants such as DTBP, AIBN and BPO showed less or no efficiency (Table 1, entries 9-11). A ratio of 1:3 for 1a and 2a was found to be ideal and the product could be obtained in excellent yield. From these experiments, we determined the optimized conditions to be: FeBr₂ (5 mol%), TBHP (2 equiv.), DCE, 60 °C, 16 h.

With the optimized conditions in hand, we started employing other substrates in this Fe-catalysed oxidative coupling of aldehydes with amides to synthesize imides. First of all, various aldehydes were employed to couple with N-benzylacetamide 1a. The results are summarized in Scheme 1. Benzaldehyde substituted with alkyl groups, such as o- and p-Me, reacted smoothly to afford the corresponding imides in good yields (Scheme 1, 3ab and 3ac). Normally, Fe salts have been reported to react with the aromatic



Scheme 1 Substrate scope of Fe-catalysed oxidative coupling of amide with various aldehydes.^a The reaction was carried out with 1 (0.50 mmol), 2 (1.50 mmol), TBHP (1.0 mmol of a 70% aqueous solution), FeBr₂ (0.025 mmol), DCE (2.0 mL), 60 °C, 16 h, Ar. Yields shown are for isolated products. ^b The remainder of the starting materials was observed.

C-I bond.¹² However, the benzaldehyde bearing iodine group could be well tolerated in this oxidative coupling reaction (Scheme 1, 3ah). Other halo substituents, such as F, Cl, and Br, were also well tolerated (Scheme 1, 3ad, 3ae, 3af, 3ag, 3ai, and 3aj). These C-X groups provided the possibility for further functionalization. The benzaldehyde bearing o-Br afforded a relatively low yield, which may result from the steric hindrance effect (Scheme 1, 3ae). This orthoposition effect has also been observed in the benzaldehydes bearing p-Cl, p-F, o-Cl, and o-F (Scheme 1, 3af, 3ag, 3ai, and 3aj). The benzaldehyde derivative bearing an electron-withdrawing substituent such as the CF3 group gave moderate yield (Scheme 1, 3ak). The benzaldehyde derivative bearing an electron-donating substituent such as the OMe group afforded a lower yield (Scheme 1, 3al). It was noteworthy that the reaction with the aliphatic aldehyde also proceeded well under the standard conditions to give the corresponding imide in a moderate yield (Scheme 1, 3am).

Encouraged by these promising results, we further applied the optimized conditions to test the substrate scope of amides. Aromatic amides afforded the corresponding imides in good yields (Scheme 2, 3ba-3fa). Aromatic amides with electrondonating substituents such as Me and OMe worked well under the optimized reaction conditions (Scheme 2, 3ca, 3da, 3ea, and 3fa).



Scheme 2 Substrate scope of Fe-catalysed oxidative coupling of amides with benzaldehyde. ^a The reaction was carried out with **1** (0.50 mmol), **2** (1.50 mmol), TBHP (1.0 mmol of a 70% aqueous solution), FeBr₂ (0.025 mmol), DCE (2 mL), 60 °C, 16 h, Ar. Yields shown are for isolated products. ^b The remainder of the starting materials was observed.

It is worth noting that an *o*-Me substituent has little negative steric effect, affording the coupling product in an excellent yield (Scheme 2, **3ca** and **3fa**). Unfortunately, aromatic amides with electron-withdrawing substituents were not suitable for the reaction under the standard conditions. Aliphatic amides proceeded well in this oxidative coupling reaction (Scheme 2, **3ga**, **3ha** and **3ia**). The desired product was obtained in 67% isolated yield when a cyclic amide was applied (Scheme 2, **3ja**). To our delight, a substrate with the propionyl group also worked well in this transformation (Scheme 2, **3la**).

When investigating the mechanism of this Fe-catalysed oxidative coupling of amides with aldehydes, the single electron transfer (SET) process is considered. Generally, the aldehyde could be easily converted to the corresponding acyl radical in the presence of peroxides. Therefore, a radical-trapping experiment was carried out. A 78% isolated yield of TEMPO-adduct aldehyde 4 was obtained when TEMPO was introduced into the reaction, while the formation of **3aa** was completely suppressed (eqn (3)). This result provided good evidence that the acyl radical was formed under the standard conditions.



To elucidate the role of $FeBr_2$ in the reaction, the reaction between **1b** and **2a** in the presence of a catalytic amount of Br_2 was conducted. However, only a 7% GC yield of the desired product was obtained (eqn (4)), thus providing evidence that the iron cation also played an important role in the catalytic cycle and promotes the reaction efficiency.

To further assess the nature of the iron cation, the reaction between **1b** and **2a** with FeBr₂ or FeBr₃ as the precatalyst was investigated. The results are shown in eqn (5). Using FeBr₂ as the catalyst precursor, the reaction provided the desired product in an 89% GC yield. The reaction using FeBr₃ as the catalyst precursor gave an 88% GC yield. Similar results indicated that Fe(\mathfrak{m}) might be involved in the catalytic cycle for this oxidative coupling.

$$\begin{array}{c} O \\ N \\ H \\ H \\ 1b \\ 1b \\ 2a \\ \hline Fe salt (5 mol%) \\ \hline TBHP (2 equiv) \\ DCE, 60 \ ^{\circ}C, 16 \ h \\ Ph \\ 3ba \\ \hline Fe salt: FeBr_{2}, 89\% \\ \hline FeBr_{3}, 88\% \end{array}$$

Based on the above results, a plausible mechanism was proposed in Scheme 3. In the first step, $FeBr_2$ was oxidized by TBHP to generate a Fe(m) species, bromine and an alkyloxy radical which then abstracts hydrogen from the aldehyde to generate the acyl radical. Subsequently, the acyl radical abstracts a bromine atom from bromine to produce the acyl bromide. The addition of an amide to acyl bromide afforded the desired product along with an equivalent amount of hydrogen bromide which may be oxidized by TBHP to recover the bromide source.

We have developed the first Fe-catalysed oxidative coupling of amides with aldehydes to construct imides. By using a simple catalytic system consisting of FeBr₂,¹³ TBHP, and DCE, a variety of amides and aldehydes could be directly transformed into imides in moderate to good yields. Moreover, various



Scheme 3 Proposed mechanism.

functional groups were tolerated under the optimized conditions. This work opens up a new approach for the construction of imides. Preliminary mechanistic studies revealed that benzoyl halide might be formed from the aldehyde and a catalytic amount of halide source. Further studies on the mechanism are currently underway and will be reported in due course.

This work was supported by the 973 Program (2012CB725302), the National Natural Science Foundation of China (21025206, 21272180 and 21302148), and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1030) and the Research Fund for the Doctoral Program of Higher Education of China (20120141130002).

Notes and references

- 1 (a) J. A. Ashenhurst, Chem. Soc. Rev., 2010, 39, 540-548; (b) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, Chem. Soc. Rev., 2011, 40, 5068-5083; (c) O. Daugulis, H. Q. Do and D. Shabashov, Acc. Chem. Res., 2009, 42, 1074-1086; (d) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn and B. DeBoef, Org. Lett., 2007, 9, 3137-3139; (e) C. Jia, T. Kitamura and Y. Fujiwara, Acc. Chem. Res., 2001, 34, 633-639; (f) A. A. Kantak, S. Potavathri, R. A. Barham, K. M. Romano and B. DeBoef, J. Am. Chem. Soc., 2011, 133, 19960–19965; (g) J. Le Bras and J. Muzart, Chem. Rev., 2011, 111, 1170-1214; (h) C. J. Li, Acc. Chem. Res., 2009, 42, 335-344; (i) C. Liu, H. Zhang, W. Shi and A. Lei, Chem. Rev., 2011, 111, 1780-1824; (j) G. P. McGlacken and L. M. Bateman, Chem. Soc. Rev., 2009, 38, 2447-2464; (k) S. Potavathri, A. S. Dumas, T. A. Dwight, G. R. Naumiec, J. M. Hammann and B. Deboef, Tetrahedron Lett., 2008, 49, 4050-4053; (l) S. Potavathri, A. Kantak and B. DeBoef, Chem. Commun., 2011, 47, 4679-4681; (m) S. Potavathri, K. C. Pereira, S. I. Gorelsky, A. Pike, A. P. LeBris and B. DeBoef, J. Am. Chem. Soc., 2010, 132, 14676-14681.
- 2 (a) A. N. Campbell and S. S. Stahl, Acc. Chem. Res., 2012, 45, 851–863;
 (b) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, Chem. Soc. Rev., 2011, 40, 5068–5083; (c) T. A. Ramirez, B. Zhao and Y. Shi, Chem. Soc. Rev., 2012, 41, 931–942; (d) Z. Shi, C. Zhang, C. Tang and N. Jiao, Chem. Soc. Rev., 2012, 41, 3381–3430; (e) C. Zhang, C. Tang and N. Jiao, Chem. Soc. Rev., 2012, 41, 3464–3484.
- 3 (a) J. J. Bozell and L. S. Hegedus, J. Org. Chem., 1981, 46, 2561–2563;
 (b) X. Chen, C. E. Goodhue and J. Q. Yu, J. Am. Chem. Soc., 2006, 128, 12634–12635;
 (c) K. Ekoue-Kovi and C. Wolf, Chem. Eur. J., 2008, 14, 6302–6315;
 (d) D. Monguchi, T. Fujiwara, H. Furukawa and A. Mori, Org. Lett., 2009, 11, 1607–1610;
 (e) Y. Suto, N. Yamagiwa and M. Mori, Org. Lett., 2009, 12, 1607–1610;
 (e) Y. Suto, N. Yamagiwa and M. Mori, Org. Lett., 2009, 12, 1607–1610;
 (f) Y. Suto, N. Yamagiwa and M. Mori, Org. Lett., 2009, 12, 1607–1610;
 (f) Y. Suto, N. Yamagiwa and M. Mori, Org. Lett., 2009, 12, 1607–1610;
 (f) Y. Suto, N. Yamagiwa and M. Mori, Org. Lett., 2009, 11, 1607–1610;
 (f) Y. Suto, N. Yamagiwa and M. Mori, Org. Lett., 2009, 11, 1607–1610;
 (f) Y. Suto, N. Yamagiwa and M. Mori, Org. Lett., 2009, 11, 1607–1610;
 (f) Y. Suto, N. Yamagiwa and M. Mori, Org. Lett., 2009, 11, 1607–1610;
 (f) Y. Suto, N. Yamagiwa and Yam

- Y. Torisawa, *Tetrahedron Lett.*, 2008, **49**, 5732–5735; (*f*) Q. Wang and S. L. Schreiber, *Org. Lett.*, 2009, **11**, 5178–5180.
- 4 (a) C. Liang, F. Robert-Peillard, C. Fruit, P. Mueller, R. H. Dodd and P. Dauban, Angew. Chem., Int. Ed., 2006, 45, 4641–4644; (b) G. Liu, G. Yin and L. Wu, Angew. Chem., Int. Ed., 2008, 47, 4733–4736; (c) J. L. Brice, J. E. Harang, V. I. Timokhin, N. R. Anastasi and S. S. Stahl, J. Am. Chem. Soc., 2005, 127, 2868–2869; (d) K. W. Fiori and J. Du Bois, J. Am. Chem. Soc., 2005, 127, 2868–2869; (d) K. W. Fiori and J. Du Bois, J. Am. Chem. Soc., 2007, 129, 562–568; (e) S. A. Reed and M. C. White, J. Am. Chem. Soc., 2008, 130, 3316–3318; (f) V. I. Timokhin, N. R. Anastasi and S. S. Stahl, J. Am. Chem. Soc., 2003, 125, 12996–12997; (g) V. I. Timokhin and S. S. Stahl, J. Am. Chem. Soc., 2005, 127, 17888–17893; (h) S.-M. Au, J.-S. Huang, C.-M. Che and W.-Y. Yu, J. Org. Chem., 2000, 65, 7858–7864; (i) X.-Q. Yu, J.-S. Huang, X.-G. Zhou and C.-M. Che, Org. Lett., 2000, 2, 2233–2236; (j) Y. Zhang, H. Fu, Y. Jiang and Y. Zhao, Org. Lett., 2007, 9, 3813–3816; (k) T. Hosokawa, M. Takano, Y. Kuroki and S. Murahashi, Tetrahedron Lett., 1992, 33, 6643–6646.
- J. Chan, K. D. Baucom and J. A. Murry, J. Am. Chem. Soc., 2007, 129, 14106–14107; (b) F. Ragaini, T. Longo and S. Cenini, J. Mol. Catal. A: Chem., 1996, 110, L171–L175; (c) J. M. Lee, D.-S. Ahn, D. Y. Jung, J. Lee, Y. Do, S. K. Kim and S. Chang, J. Am. Chem. Soc., 2006, 128, 12954–12962; (d) H.-Y. Thu, W.-Y. Yu and C.-M. Che, J. Am. Chem. Soc., 2006, 128, 9048–9049.
- 6 (a) L. Wang, H. Fu, Y. Jiang and Y. Zhao, *Chem. Eur. J.*, 2008, 14, 10722–10726; (b) Y. J. Bian, C. Y. Chen and Z. Z. Huang, *Chem. Eur. J.*, 2013, 19, 1129–1133.
- 7 (a) A. B. C. Simas, D. L. de Sales and K. C. Pais, *Tetrahedron Lett.*, 2009, 50, 6977–6980; (b) M. Hamaguchi, N. Tomida and Y. Iyama, J. Org. Chem., 2007, 72, 1326–1334.
- 8 (a) Y. D. Reddy, P. P. Kumar, B. R. Devi, P. K. Dubey and Y. B. Kumari, *Lett. Drug Des. Discovery*, 2013, 10, 226–238;
 (b) J. Zhang and S. H. Hong, *Org. Lett.*, 2012, 14, 4646–4649.
- 9 (a) X. J. Jin, K. Yamaguchi and N. Mizuno, *Chem. Lett.*, 2012, 41, 866–867;
 (b) Y. Y. Yang, G. Wang, X. H. Cao, X. L. Yan and L. G. Chen, *J. Chem. Res.*, 2011, 657–658; (c) Y. Y. Yang, G. Wang, X. H. Cao, X. L. Yan and L. G. Chen, *J. Chem. Res.*, 2011, 657–658; (d) J. Sperry, *Synthesis*, 2011, 3569–3580.
- 10 J. Wang, C. Liu, J. Yuan and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 2256–2259.
- 11 Z. Huang, L. Jin and A. Lei, Chin. J. Org. Chem., 2011, 6, 775-783.
- 12 (a) B. D. Sherry and A. F. Rstner, Acc. Chem. Res., 2008, 41, 1500–1511; (b) M. Carril, A. Correa and C. Bolm, Angew. Chem., Int. Ed., 2008, 47, 4862–4865; (c) O. Bistri, A. Correa and C. Bolm, Angew. Chem., Int. Ed., 2008, 47, 586–588; (d) L. Jin, X. Luo and A. Lei, Chin. J. Chem., 2012, 70, 1538–1542.
- 13 (a) T. Xu, Q. Yang, D. Li, J. Dong, Z. Yu and Y. Li, *Chem. Eur. J.*, 2010, **16**, 9264–9272; (b) A. Gutierrez-Bonet, A. Flores-Gaspar and R. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 12576–12579; (c) T. Zhang and W. Bao, *J. Org. Chem.*, 2013, **78**, 1317–1322.