RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 28225

Received 2nd May 2014
Accepted 17th June 2014

DOI: 10.1039/c4ra04012k

www.rsc.org/advances

N-heterocyclic carbene-catalyzed oxidation of aldehydes for the synthesis of amides *via* phenolic esters†

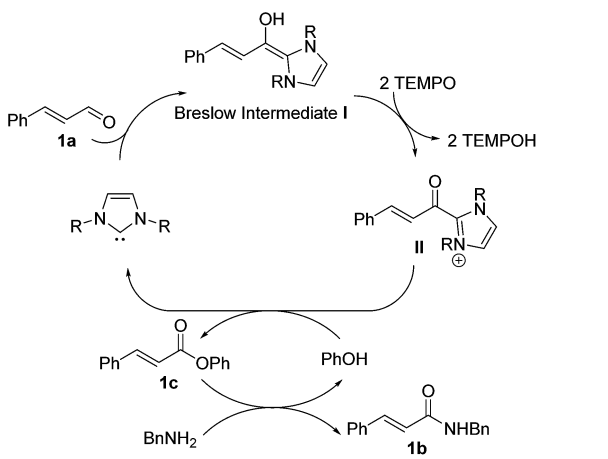
Miran Ji,[a] Seungyeon Lim[a] and Hye-Young Jang*[ab]

N-heterocyclic carbene-catalyzed oxidation using TEMPO is reported for the conversion of aldehydes to amides. A wide range of amides were synthesized in good yields (up to 72%) *via* a one-pot, sequential protocol involving oxidative esterification of aldehydes and subsequent aminolysis. To promote efficient aminolysis, various alkoxide leaving groups were evaluated.

The amide group is a common feature in many important compounds including pharmaceuticals, and in peptide bonds, and polymers (*e.g.*, nylon and aramid).[1] As a result, a variety of synthetic methods have been developed over the years to form amides, including use of coupling reagents, metal-catalysts, and metal-free conditions.[2–7] Amongst these, our attention has been drawn to carbene-catalyzed amidation conditions because of the environmental benefits of metal-free conditions. Compared to carbene-catalyzed esterification of aldehydes,[8–10] carbene-catalyzed amide formation from aldehydes is limited because of the competing imine formation. Based on Studer's report on carbene-catalyzed oxidative amidation, imine formation can be reduced using a sequential approach of carbene-catalyzed reactive ester formation, followed by aminolysis of the esters.[6a,11] Although most carbene-catalyzed reactions required higher catalyst loadings and showed lower turnovers compared to those of the metal-catalyzed reactions, continuous studies of carbene-catalyzed reactions would provide efficient metal-free synthetic protocols.

We recently reported a carbene-catalyzed oxidation of aldehydes using 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) to afford a diverse range of esters and thioesters.[12] Under Studer's conditions, the stable TEMPO-ester formed readily, thereby making formation of the other esters and thioesters impossible.[10a] However, we found that we could modulate the formation of various esters and thioesters without forming the TEMPO-esters as the product. Herein, we report the use of carbene catalysts and TEMPO oxidant for the tandem oxidative esterification of aldehydes-aminolysis, to afford a diverse range of amides from aldehydes. A possible mechanism is proposed in Scheme 1. Based on our previous work, aldehyde **1a** undergoes oxidative esterification *via* Breslow intermediate **I** to afford phenolic ester **1c**. Subsequent aminolysis of **1c** provides desired amide **1b**.

Optimization results are listed in Table 1. Initially, the oxidative esterification of cinnamaldehyde **1a** with various alcohols, followed by aminolysis using benzyl amine was investigated. Alcohols (1 equiv.) were reacted with cinnamaldehyde **1a** (1 equiv.) in the presence of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 10 mol%), TEMPO (2 equiv.) in toluene at 100 °C for 4 h, followed by addition of benzyl amine (2 equiv.) and the mixture being stirred at 40 °C for 18 h. As shown in entry 1 of Table 1, reaction of **1a** with isopropyl alcohol failed to form the desired amide **1b**. Use of



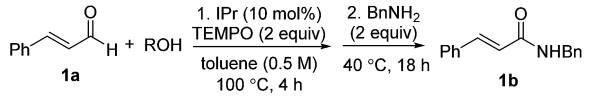
Scheme 1 N-heterocyclic carbene-catalyzed amides synthesis from aldehydes.

[a]*Division of Energy Systems Research, Ajou University, Suwon 443-749, Korea. E-mail: hyjang2@ajou.ac.kr; Fax: +82 31 219 1615; Tel: +82 31 219 2555*

[b]*Korea Carbon Capture & Sequestration R&D Center, Deajeon 305-343, Korea*

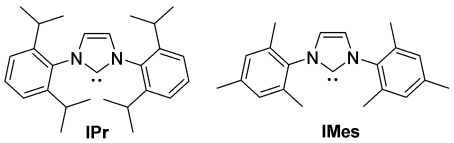
† Electronic supplementary information (ESI) available: Detailed experimental and spectral analysis for new compounds. See DOI: 10.1039/c4ra04012k

Table 1 Optimization of carbene-catalyzed amidation to form **1b**[b]



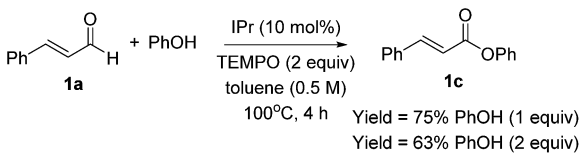
Entry	Carbene	TEMPO	ROH	pK_a of ROH	Yield[a] (**1b**)
1	IPr (10 mol%)	2 equiv.	^{i}PrOH	17	0%
2	IPr (10 mol%)	2 equiv.	CF_3CH_2OH	12.4	34%
3	IPr (10 mol%)	2 equiv.	HFIP	9.3	57%
4	IPr (10 mol%)	2 equiv.	PhOH	10.0	60%
5	IPr (10 mol%)	2 equiv.	$p$$NO_2$–PhOH	7.2	0%
6	IPr (10 mol%)	2 equiv.	F_5-PhOH	5.5	0%
7	IPr (10 mol%)	1.5 equiv.	PhOH	10.0	44%
8	IPr (5 mol%)	2 equiv.	PhOH	10.0	44%
9	IMes (10 mol%)	2 equiv.	PhOH	10.0	43%

[a] Isolated yield. [b] Experimental: TEMPO (1.0 mmol) and IPr (0.05 mmol) was added to a solution of **1a** (0.5 mmol) and ROH (0.5 mmol) in toluene (0.5 M) under nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 4 h. Then, benzylamine (1.0 mmol) was added to the reaction vessel and the reaction mixture was stirred at 40 °C for 18 h.



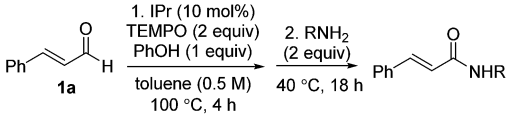
fluorinated alcohols improved the yield to 34% and 57% (entries 2 and 3). It was proposed that the basicity of the conjugated base of the alcohol could affect the progress of the aminolysis step, as the oxidative esterification of **1a** to form the corresponding esters was completed within 4 h. Thus, the more basic isopropoxide group is considered as a poorer leaving group, and therefore no amide formation was observed. By considering the pK_a of the alcohols, phenol, with a similar pK_a to that of hexafluoroisopropyl alcohol (HFIP) was tested (entry 4).[13] As expected, these reactions, which proceeded *via* the phenolic and hexafluoroisopropyl ester respectively, afforded the similar yields of product (entries 3 and 4). In addition to phenol, $p$$NO_2$–phenol and pentafluorophenol (F_5-PhOH) were tested; however, these failed to form desired amide **1b** (entries 5 and 6). In the case of the electron-deficient phenols, the intermediate esters were not formed because of the low nucleophilicity of the phenol derivatives. It was found that the amount of TEMPO could be reduced to 1.5 equiv. and afforded amide **1b** in 44% yield (entry 7). The IPr carbene catalyst loading was also reduced to 5 mol%; however, this led to a decrease in the yield of **1b** (entry 8). Finally, an alternative carbene catalyst (IMes) was investigated but unfortunately this also led to a lower yield of **1b** compared to that with the IPr catalyst (43%, entry 9).[14] In the absence of carbene catalysts, either phenolic ester **1c** or amide **1b** was not formed. Without TEMPO, saturated amide **1d** was formed in 69% yield, implying redox-esterification instead of oxidative esterification occurred in the absence of TEMPO.[15] Based on our previous reports regarding the oxidative esterification of **1a** with phenol,[12] it was expected that excessive amounts of phenol would not increase the yield of esters. This was confirmed by reacting **1a** with 1 and 2 equiv. of phenol which afforded **1c** in a comparable 75% and 63% yields, respectively (Scheme 2). Subsequently, the stoichiometry of phenol was fixed at 1 equiv. with respect to **1a**.

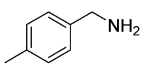
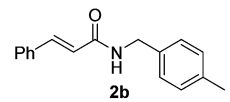
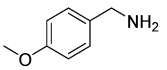
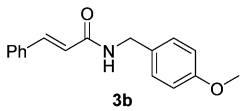
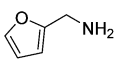
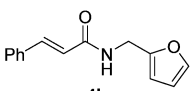
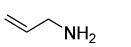
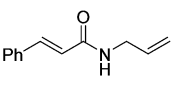
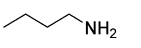
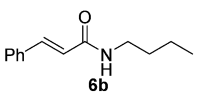
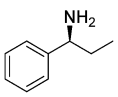
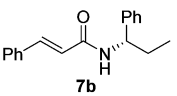
Next, the substrate scope was investigated by employing a diverse range of amines and aldehydes (Tables 2 and 3). The reaction of cinnamaldehyde with various amines was conducted using the optimized reaction conditions. Electron-rich benzyl amines (p-methyl benzyl amine and p-methoxy benzyl amine) performed well in the reaction with cinnamaldehyde, to afford **2b** and **3b** in 55% and 59% yield, respectively (Table 2, entries 1



Scheme 2 Oxidative esterification of **1a** with phenol.

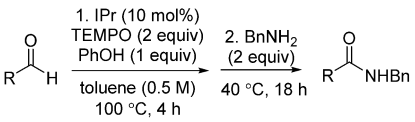
Table 2 The reactions of cinnamaldehyde with various amines[b]

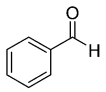
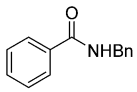
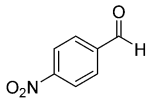
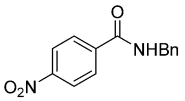
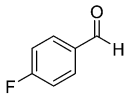
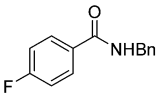
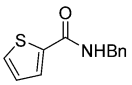
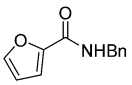
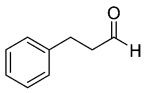
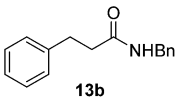
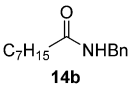


Entry	Amine	Product	Yield[a]
1		 **2b**	55%
2		 **3b**	59%
3		 **4b**	41%
4		 **5b**	50%
5		 **6b**	52%
6		 **7b**	60%

[a] Isolated yield. [b] Experimental: TEMPO (1.0 mmol) and IPr (0.05 mmol) was added to a solution of **1a** (0.5 mmol) and PhOH (0.5 mmol) in toluene (0.5 M) under nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 4 h. Then, benzylamine (1.0 mmol) was added to the reaction vessel and the reaction mixture was stirred at 40 °C for 18 h.

Table 3 The reactions of various aldehydes with benzyl amine[b]



Entry	Amine	Product	Yield[a]
1		 **8b**	55%
2		 **9b**	55%
3		 **10b**	56%
4		 **11b**	54%
5		 **12b**	72%
6		 **13b**	45%
7		 **14b**	38%

[a] Isolated yield. [b] Experimental: TEMPO (1.0 mmol) and IPr (0.05 mmol) was added to a solution of aldehyde (0.5 mmol) and PhOH (0.5 mmol) in toluene (0.5 M) under nitrogen atmosphere. The reaction mixture was stirred at 100 °C for 4 h. Then, benzylamine (1.0 mmol) was added to the reaction vessel and the reaction mixture was stirred at 40 °C for 18 h.

and 2). Heteroaromatic amine led to the formation of **4b** in a slightly reduce yield (41%, entry 3). The reactions of cinnamaldehyde with allyl amine and aliphatic amine proceeded well to afford **5b** (50%) and **6b** (52%) (entries 4 and 5). An amide formation using sterically hindered α-ethylbenzyl amine was also successful and afforded **7b** in 60% yield (entry 6).

Next, the scope of aldehyde was investigated for amide formation using benzyl amine (Table 3). Benzaldehyde and electron-deficient benzaldehydes (*p*NO_2-substituted and *p*fluoro-substituted) reacted with benzyl amine to provide **8b** (55%), **9b** (55%), and **10b** (56%), respectively (entries 1–3). Thiophenyl carboxaldehyde and furfural reacted well to afford **11b** and **12b** in 54% and 72% yield, respectively (entries 4 and 5). In addition to aromatic aldehydes, aliphatic aldehydes were also subjected to the reaction conditions; however, this afforded aliphatic amide **13b** and **14b** in a reduced 45% and 38% yield, respectively (entries 6 and 7).

Conclusions

In conclusion, we have expanded our NHC-catalyzed oxidative coupling using TEMPO for the synthesis of a range of amides from aldehydes. To address the previous imine formation issues, we utilized a tandem reaction protocol involving NHC-catalyzed oxidative phenolic ester formation followed by aminolysis. The optimum alcohol for the ester formation and aminolysis was chosen based on pK_a values. As a result, phenol (pK_a = 10.0) was found to be the most favourable alcohol for the amide formation. Under optimized conditions, a diverse range of aromatic and aliphatic aldehydes and amines were coupled to form the desired amides in modest to good yield *via* the intermediate esters.

Acknowledgements

This study was supported by the Korea Research Foundation (no. 2009-0094046 and 2013008819) and the Korea CCS R&D Center (KCRC) grant funded by the Korea Government (Ministry of Education, Science and Technology) (no. 2012-0008935).

Notes and references

1 (*a*) A. K. Ghose, V. N. Viswanadhan and J. J. Wendoloski, *J. Comb. Chem.*, 1999, **1**, 55–68; (*b*) J. W. Bode, *Curr. Opin. Drug Discovery Dev.*, 2006, **9**, 765–775; (*c*) T. Cupido, J. Tulla-Puche, J. Spengler and F. albericio, *Curr. Opin. Drug Discovery Dev.*, 2007, **10**, 768–783.

2 For selected review articles for the synthesis of amides, see: (*a*) S.-Y. Han and Y.-A. Kim, *Tetrahedron*, 2004, **60**, 2447–2467; (*b*) C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827–10852; (*c*) K. Ekoue-Kovi and C. Wolf, *Chem.–Eur. J.*, 2008, **14**, 6302–6315; (*d*) A. El-Faham and F. Albericio, *Chem. Rev.*, 2011, **111**, 6557–6602; (*e*) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471–479; (*f*) S. Roy, S. Roy and G. W. Gribble, *Tetrahedron*, 2012, **68**, 9867–9923.

3 For selected articles for the transition metal-catalyzed amidation of alcohols, see: (*a*) C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790–792; (*b*) L. U. Nordstrøm, H. Vogt and R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672–17673; (*c*) S. C. Ghosh, S. Muthaiah, Y. Zhang, X. Xu and S. H. Hong, *Adv. Synth. Catal.*, 2009, **351**, 2643–2649; (*d*) S. Muthaiah, S. C. Ghosh, J.-E. Jee, C. Chen, J. Zhang and S. H. Hong, *J. Org. Chem.*, 2010, **75**, 3002–3006; (*e*) Y. Wang, D. Zhu, L. Tang, S. Wang and Z. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8917–8921; (*f*) J.-F. Soule, H. Miyamura and S. Kovayashi, *J. Am. Chem. Soc.*, 2011, **133**, 18550–18553; (*g*) S. Kegnæs, J. Mielby, U. V. Mentzel, T. Jensen, P. Fristrup and A. Riisager, *Chem. Commun.*, 2012, **48**, 2427–2429; (*h*) S. C. Ghosh,

J. S. Y. Ngiam, A. M. Seayad, D. T. Tuan, C. W. Johannes and A. Chen, *Tetrahedron Lett.*, 2013, **54**, 4922–5492.

4 For selected articles for the transition metal-catalyzed oxidative amidation of aldehydes, see: (*a*) A. Tillack, I. Rudloff and M. Beller, *Eur. J. Org. Chem.*, 2001, 523–528; (*b*) W.-J. Yoo and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 13064–13065; (*c*) J. W. W. Chang and P. W. H. Chan, *Angew. Chem., Int. Ed.*, 2008, **47**, 1138–1140; (*d*) S. Seo and T. J. Marks, *Org. Lett.*, 2008, **10**, 317–319; (*e*) L. Wang, H. Fu, Y. Jiang and Y. Zhao, *Chem.–Eur. J.*, 2008, **14**, 10722–10726; (*f*) C. Qian, X. Zhang, J. Li, F. Xu, Y. Zhang and Q. Shen, *Organometallics*, 2009, **28**, 3856–3862; (*g*) J. Li, F. Xu, Y. Zhang and Q. Shen, *J. Org. Chem.*, 2009, **74**, 2575–2577; (*h*) S. C. Ghosh, J. S. Y. Ngiam, C. L. L. Chai, A. M. Seayad, T. T. Dang and A. Chen, *Adv. Synth. Catal.*, 2012, **354**, 1407–1412; (*i*) S. C. Ghosh, J. S. Y. Ngiam, A. M. Seayad, D. T. Tuan, C. L. L. Chai and A. Chen, *J. Org. Chem.*, 2012, **77**, 8007–8015; (*j*) C. Zhang, X. Zong, L. Zhang and N. Jiao, *Org. Lett.*, 2012, **14**, 3280–3283; (*k*) H. Yao and K. Yamamoto, *Chem.–Asian J.*, 2012, **7**, 1542–1545.

5 For the oxidative amidation of aldehydes in the absence of carbene catalysts, see: (*a*) K. Ekoue-Kovi and C. Wolf, *Org. Lett.*, 2007, **9**, 3429–3432; (*b*) J.-J. Shie and J.-M. Fang, *J. Org. Chem.*, 2003, **68**, 1158–1160; (*c*) K. Xu, Y. Hu, S. Zhang, Z. Zhan and Z. Wang, *Chem. Eur. J.*, 2012, **18**, 9793–9797.

6 For carbene-catalyzed oxidative amidation of aldehydes, see: (*a*) S. D. Sarkar and A. Studer, *Org. Lett.*, 2010, **12**, 1992–1995; (*b*) S. Kuwano, S. Harada, R. Oriez and K.-i. Yamada, *Chem. Commun.*, 2012, **48**, 145–147.

7 For carbene-catalyzed redox amidation of aldehydes, see: (*a*) H. U. Vora and T. Rovis, *J. Am. Chem. Soc.*, 2007, **129**, 13796–13797; (*b*) J. W. Bode and S. S. Sohn, *J. Am. Chem. Soc.*, 2007, **129**, 13798–13799; (*c*) H. U. Vora, P. Wheeler and T. Rovis, *Adv. Synth. Catal.*, 2012, **354**, 1617–1639.

8 For reviews of NHC-catalyzed reactions, see: (*a*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534–541; (*b*) K. Zeitler, *Angew. Chem., Int. Ed.*, 2005, **44**, 7506–7510; (*c*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655; (*d*) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988–3000; (*e*) H. U. Vora and T. Rovis, *Aldrichimica Acta*, 2011, **44**, 3; (*f*) J. Mahatthananchai and J. W. Bode, *Chem. Sci.*, 2012, **3**, 192–197; (*g*) S. De Sarkar, A. Biswas, R. C. Samanta and A. Studer, *Chem.–Eur. J.*, 2013, **19**, 4664–4678, Carbene-catalyzed oxidation.

9 For carbene-catalyzed oxidation of aldehydes to carboxylic acids, see: P.-C. Chiang and J. W. Bode, *Org. Lett.*, 2011, **13**, 2422–2425.

10 For carbene-catalyzed oxidative esterification of aldehydes, see: (*a*) J. Guin, S. De sarkar, S. Grimme and A. Studer, *Angew. Chem., Int. Ed.*, 2008, **47**, 8727–8730; (*b*) B. E. Maki and K. A. Scheidt, *Org. Lett.*, 2008, **10**, 4331–4334; (*c*) C. Noonan, L. Baragwanath and S. J. Cannon, *Tetrahedron Lett.*, 2008, **49**, 4003–4006; (*d*) B. E. Maki, A. Chan, E. M. Phillips and K. A. Scheidt, *Tetrahedron*, 2009, **65**, 3102–3109; (*e*) S. De Sarkar, S. Grimme and A. Studer, *J. Am. Chem. Soc.*, 2010, **132**, 1190–1191; (*f*) C. A. Rose and K. Zeitler, *Org. Lett.*, 2010, **12**, 4552–4555; (*g*) B. Maji, S. Vedachalan, X. Ge, S. Cai and X.-W. Liu, *J. Org. Chem.*, 2011, **76**, 3016–3023; (*h*) E. E. Finney, K. A. Ogawa and A. J. Boydston, *J. Am. Chem. Soc.*, 2012, **134**, 12374–12377; (*i*) P. Arde, B. T. Ramanjaneyulu, V. Reddy, A. Saxena and R. V. Anand, *Org. Biomol. Chem.*, 2012, **10**, 848–851; (*j*) T. Uno, T. Inokuma and Y. Takemoto, *Chem. Commun.*, 2012, **48**, 1901–1903; (*k*) I. N. C. Kiran, K. Lalwani and A. Sudalai, *RSC Adv.*, 2013, **3**, 1695–1698; (*l*) L. Möhlmann, S. Ludwig and S. Blechert, *Beilstein J. Org. Chem.*, 2013, **9**, 602–607; (*m*) J. Zhao, C. Mück-Lichtenfeld and A. Studer, *Adv. Synth. Catal.*, 2013, **355**, 1098–1106.

11 For carbene-catalyzed amidation of unactivated esters, see: M. Movassaghi and M. A. Schmidt, *Org. Lett.*, 2005, **7**, 2453–2456.

12 M. Ji, X. Wang, Y. N. Lim, Y.-W. Kang and H.-Y. Jang, *Eur. J. Org. Chem.*, 2013, 7881–7885.

13 For references presenting pK_a values of alcohols, see: (*a*) W. A. Sheppard, *J. Am. Chem. Soc.*, 1970, **92**, 5419–5422; (*b*) L. Eberson, M. P. Hartshorn, O. Persson and F. Radner, *Chem. Commun.*, 1996, 2105–2112; (*c*) Y.-M. Shen, W.-L. Duan and M. Shi, *Adv. Synth. Catal.*, 2003, **345**, 337–340.

14 In our previous publication (ref. 12), the IPr carbene showed better activitity than the IMes carbene in the oxidative esterification of aldehydes. However, in the one-pot reaction involving oxidation of allylic alcohols and oxidative esterification, IMes showed better conversion than IPr. The catalytic activity of carbenes seems different depending on reaction conditions.

15 In the absence of TEMPO, redox esterification occurred to afford saturated amide **1d**.