ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal

A simple base-mediated amidation of aldehydes with azides†

Cite this: DOI: 10.1039/c2cc37289d

Received 6th October 2012,
Accepted 23rd November 2012

DOI: 10.1039/c2cc37289d

www.rsc.org/chemcomm

Sameer S. Kulkarni, Xiangdong Hu and Roman Manetsch*

A practical and efficient amidation reaction involving aromatic aldehydes and various azides under mild conditions is described. A broad spectrum of functional groups was tolerated, and the amides were synthesized in moderate to excellent yields, presenting an attractive alternative to the currently available synthetic methods.

The amide bond serves as one of the nature's most fundamental functional groups. Indeed, it is an integral component of a large number of organic and biological molecules such as pharmaceuticals, natural products, peptides, and proteins. Traditionally, the amide functionality is incorporated through a reaction of an amine with either an activated carboxylic acid (generally acid halides or anhydrides) or by an activation using carbodiimide coupling reagents. However, several innovative approaches have been developed in the past decade, which include the Staudinger reaction,[1] the α-bromo nitroalkane–amine coupling,[2] the native chemical ligation,[3] the thio acid–azide amidation,[4] the alkyne–sulfonyl azide coupling,[5] the coupling of acyltrifluoroborates with hydroxylamines[6] or azides,[7] the Au/DNA-catalyzed amidation from alcohols and amines,[8] the amino-carbonylation of aryl halides,[9] and the Pd catalyzed coupling of aryl halides with isocyanides.[10] Additionally, numerous one-pot oxidative amidation methods have been reported wherein, aldehydes,[11] alcohols[12] or alkynes[13] are oxidized using transition metal catalysts and treated with amines yielding corresponding amides. Meanwhile, some environmentally benign metal-free amidation procedures employing silyl reagents[14] or oxidants like sodium chlorite,[15] peroxide[16] have also been exploited.

Another important approach to amides is the Schmidt reaction,[17] involving ketones and hydrazoic acid. Aube and co-workers have reported an intramolecular Schmidt reaction of cyclic ketones to construct *N*-substituted lactams in which hydrazoic acid was replaced by an alkyl azide.[18] An interesting extension of this reaction, known as the Boyer reaction,[19] was first reported[19a] in 1950s, wherein, two aromatic aldehydes were reacted with β-phenylethyl azide under harsh acidic conditions generating the corresponding amides in moderate yields. Strikingly, this reaction failed to afford the desired amide when benzyl or *n*-butyl azide was used. The reaction of benzyl azide is of particular interest since it leads to amidomethylarenes. In fact, a variety of therapeutic agents such as Picotamide,[20] Raltegravir[21] and others[22] are comprised of an amido-methylarene moiety. Recently, Molander *et al.* reported a synthetic route to generate these types of molecules *via* a C–C bond forming reaction between amidomethyltrifluoroborates and aryl or heteroaryl chlorides.[22c] Although a wide range of substrates were tolerated under the reported reaction conditions, a tedious 4-step sequence to access amidomethyltrifluoroborates demanding long reaction times, high temperatures and the Pd catalyst required in the following C–C bond formation are the drawbacks associated with this approach. Therefore, a simple, convenient method deprived of the aforementioned disadvantages would be of great interest. We herein unveil a straightforward protocol starting from azides and aromatic aldehydes to synthesize amidomethylarenes under mild basic conditions (Scheme 1).

Initially, the reaction conditions were screened using benzyl azide and benzaldehyde as the model substrates. The summary of these results is presented in Table 1. Surprisingly, among the non-nucleophilic bases tested, *t*-BuOK alone produced the desired amide (see the ESI†). From the set of the solvents explored, polar aprotic solvents such as THF, DMF, and DMSO proved to be suitable for this transformation, DMF offering the best results. In the course of further optimization, increasing the amount of *t*-BuOK to 2 eq. was found to significantly improve the yield of the product. Furthermore, the reaction was completed in 15 min at room temperature making it a highly efficient and practical synthetic route. Having the reaction conditions optimized, the scope of the reaction involving benzyl azide and a diverse array of aldehydes was first examined (Table 2). Aromatic aldehydes bearing electron-donating groups afforded excellent yields although an excess amount of the base was required

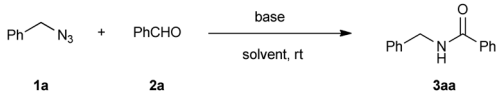
1 2 3, R = Ar, CON(alk)$_2$

Scheme 1 Reaction between azides and aromatic aldehydes yielding amides.

Department of Chemistry, University of South Florida, 4202 E Fowler Ave., Tampa, FL – 33620, USA. E-mail: manetsch@usf.edu; Tel: +1 8139747306

† Electronic supplementary information (ESI) available: Experimental section and the spectral data of all new compounds. See DOI: 10.1039/c2cc37289d

Table 1 Optimization of the reaction conditions[a]



1a 2a 3aa

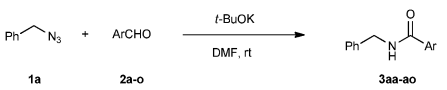
Entry	Base	Solvent	Yield[b] (%)
1	DIPEA	DMF	—
2	Cs_2CO_3	DMF	—
3	DBU	DMF	—
4	*t*-BuOK	DMF	50
5	*t*-BuOK	THF	40
6	*t*-BuOK	DMSO	23
7	*t*-BuOK[c]	DMF	72

[a] General reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), base (0.75 mmol), solvent (2.5 mL), 15 min. [b] Isolated yields based on **1a**. [c] *t*-BuOK (1.0 mmol).

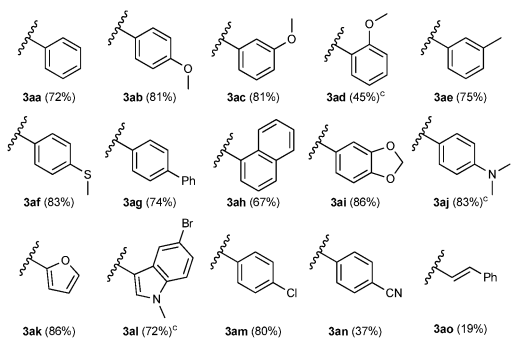
in some cases (**3ad**, **3aj**, and **3al**). Changing the position of methoxy substituent on the aromatic ring from *para* to *meta* did not affect the yield (**3ab** and **3ac**). However, the amidation reaction with the sterically challenging 2-methoxybenzaldehyde offered a moderate amount of the product (**3ad**). Substrates such as 3-methylbenzaldehyde, 4-(methylthio)benzaldehyde, [1,1′-biphenyl]-4-carbaldehyde and 1-naphthaldehyde led to the formation of desired products **3ae**–**3ah** in good to excellent yields. Functional moieties like 1,3-dioxolane (**3ai**) and *N,N*-dimethylamine (**3aj**) were well tolerated as well. Heterocyclic substrates such as furan and indole derivatives provided excellent results (**3ak** and **3al**). Among aldehydes with electron-withdrawing substituents, 4-chlorobenzaldehyde exhibited great compatibility (**3am**) whereas, lower yield was obtained when 4-cyanobenzaldehyde was used (**3an**). Cinnamaldehyde, despite being a Michael acceptor, did undergo the reaction (**3ao**) albeit with poor yield. Unfortunately, the aliphatic aldehydes are not appropriate starting materials under these reaction conditions due to the presence of a more acidic α-proton.

These encouraging results prompted us to expand the scope of this reaction with respect to the azides (Table 3). Benzyl azides consisting of electron-withdrawing substituents were successfully converted to the amides **3ba**, **3ca**, and **3da** in moderate to substantial yields. Especially, the reaction of an azide incorporated on a

Table 2 Reaction of benzyl azide with various aromatic aldehydes[a,b]

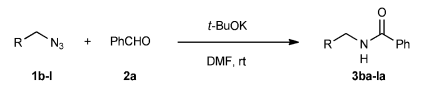


1a 2a-o 3aa-ao

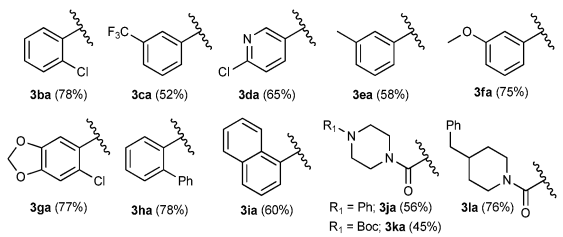


[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), *t*-BuOK (1.0 mmol), DMF (2.5 mL), 15 min. [b] Isolated yields based on **1a**. [c] *t*-BuOK (2.0 mmol).

Table 3 Reaction of various azides with benzaldehyde[a,b]



1b-l 2a 3ba-la

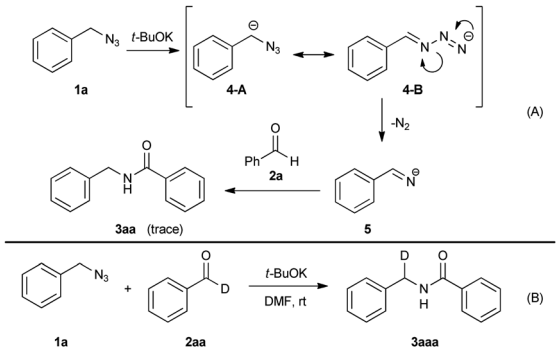


[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), *t*-BuOK (1.0 mmol), DMF (2.5 mL), 15 min. [b] Isolated yields based on **1**.

heteroaryl moiety proceeded smoothly resulting in amide **3da**. Benzyl azides containing electron-donating substituents were found to be suitable substrates for this reaction (**3ea** and **3fa**). It is noteworthy to mention that an azide with both electron-donating and withdrawing functionalities furnished the amide **3ga** in 77% yield. Substrates with sterical hindrance participated well under these reaction conditions (**3ha** and **3ia**). In pursuit of substrates other than the substituted benzyl azides, we discovered that the α-azido amides also take part in this reaction efficiently providing moderate yields for the corresponding diamides **3ja**, **3ka**, and **3la**. An acid labile Boc group was obviously unaffected (**3ka**) under these conditions, offering an advantage over the Boyer reaction. Aromatic and other aliphatic azides failed to generate corresponding amides under the reaction conditions described herein. Nevertheless, innocuous by-products (molecular nitrogen and *t*-BuOH), short reaction time, ambient temperature and easily accessible starting materials make it an attractive alternative to the contemporary synthetic routes.

Intrigued by the outcome of this study, we decided to delve into the mechanistic details of this reaction. A control experiment was designed wherein *t*-BuOK was added to a solution of azide **1a** in DMF resulting in a deprotonation followed by the loss of molecular nitrogen leading to benzylideneamide **5** (Scheme 2A). After 10 minutes of stirring, aldehyde **2a** was added to the reaction mixture. Interestingly, the desired amide **3aa** was formed only in trace amounts. On the contrary, when a mixture of azide **1a** and aldehyde **2a** in DMF was treated with *t*-BuOK, amide **3aa** was obtained in 72% yield (Table 2). This implies that the intermediate benzylideneamide **5** loses its reactivity towards aldehyde, failing to generate an amide. Whereas, if the reactive species **4** formed by addition of *t*-BuOK reacts with the aldehyde prior to the elimination of molecular nitrogen, an amide is obtained suggesting that, the nucleophilic attack of outermost nitrogen atom in species **4** on the carbonyl carbon of aldehyde is crucial for the reaction to proceed. It is worth mentioning that, the azides are generally electrophilic under basic conditions.

Based on these results, a plausible mechanism is proposed (Scheme 3). The first step would involve a deprotonation of benzyl azide, generating a highly reactive species **4**. Resonance structure **4-B** can readily react with the benzaldehyde **2a** leading to an intermediate **6** followed by a 1,5-hydride shift resulting in triazenide **7**. An intramolecular nucleophilic attack on the carbonyl carbon would produce **8**, which would be converted



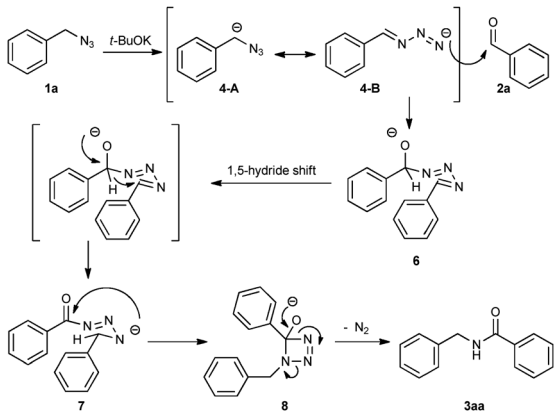
Scheme 2 Control experiments to investigate the reaction mechanism.[a] [a] Reaction conditions: **1a** (0.5 mmol), **2a** or **2aa** (0.6 mmol), *t*-BuOK (1.0 mmol), DMF (2.5 mL), 15 min.

to the amide **3aa** through a retro [2 + 2] cycloaddition or stepwise loss of molecular nitrogen.

To support our hypothesis, another experiment was conducted wherein the benzaldehyde was replaced by benzaldehyde-α-d_1 (Scheme 2B). If the reaction follows the mechanism proposed above, the deuterium should be attached to the benzylic carbon in the amide, underlining the occurrence of the proposed 1,5-hydride shift. In accordance, 50% deuterium incorporation at the benzylic position was observed by ^{1}H NMR spectroscopy, whereas ^{13}C NMR clearly showed a triplet at δ 43.96 ppm (J = 21.2 Hz) arising from the ^{13}C–^{2}H coupling. When subjected to ^{2}H NMR with 10% chloroform-d as an internal standard, a singlet at δ 4.64 ppm corresponding to the deuterium was observed (see the ESI†). In addition, the high resolution mass spectrometric analysis showed the mass corresponding to the deuterated product. Collectively, these results support the mechanism proposed in Scheme 3.

In summary, a simple, yet highly efficient methodology has been developed for the synthesis of amides starting from benzyl azides or α-azido amides and aromatic aldehydes. A wide variety of substrates were shown to deliver the desired products in moderate to excellent yields. Experiments to gain additional mechanistic insights are currently in progress.

We thank Dr. Niranjan K. Namelikonda and Dr. Raghupathi Neelarapu for fruitful discussions. We are also grateful to the James and Esther King Biomedical Research Program (NIR grant 07KN-08) for financial support.



Scheme 3 Plausible reaction mechanism of amidation.

Notes and references

1 (*a*) E. Saxon and C. R. Bertozzi, *Science*, 2000, **287**, 2007–2010; (*b*) E. Saxon, J. I. Armstrong and C. R. Bertozzi, *Org. Lett.*, 2000, **2**, 2141–2143; (*c*) B. L. Nilsson, L. L. Kiessling and R. T. Raines, *Org. Lett.*, 2000, **2**, 1939–1941; (*d*) E. Saxon, S. J. Luchansky, H. C. Hang, C. Yu, S. C. Lee and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2002, **124**, 14893–14902; (*e*) M. Kohn and R. Breinbauer, *Angew. Chem., Int. Ed.*, 2004, **43**, 3106–3116.
2 B. Shen, D. M. Makley and J. N. Johnston, *Nature*, 2010, **465**, 1027–1033.
3 P. E. Dawson, T. W. Muir, I. Clarklewis and S. B. H. Kent, *Science*, 1994, **266**, 776–779.
4 (*a*) N. Shangguan, S. Katukojvala, R. Greenburg and L. J. Williams, *J. Am. Chem. Soc.*, 2003, **125**, 7754–7755; (*b*) R. V. Kolakowski, N. Shangguan, R. R. Sauers and L. J. Williams, *J. Am. Chem. Soc.*, 2006, **128**, 5695–5702; (*c*) N. K. Namelikonda and R. Manetsch, *Chem. Commun.*, 2012, **48**, 1526–1528.
5 (*a*) S. H. Cho, E. J. Yoo, L. Bae and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 16046–16047; (*b*) M. P. Cassidy, J. Raushel and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 3154–3157.
6 A. M. Dumas, G. A. Molander and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 5683–5686.
7 G. A. Molander, J. Raushel and N. M. Ellis, *J. Org. Chem.*, 2010, **75**, 4304–4306.
8 Y. Wang, D. P. Zhu, L. Tang, S. J. Wang and Z. Y. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 8917–8921.
9 (*a*) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2007, **46**, 8460–8463; (*b*) A. Brennfuhrer, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114–4133; (*c*) X. F. Wu, H. Neumann and M. Beller, *Chem.–Eur. J.*, 2010, **16**, 9750–9753.
10 H. F. Jiang, B. F. Liu, Y. B. Li, A. Z. Wang and H. W. Huang, *Org. Lett.*, 2011, **13**, 1028–1031.
11 (*a*) W. J. Yoo and C. J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 13064–13065; (*b*) S. De Sarkar and A. Studer, *Org. Lett.*, 2010, **12**, 1992–1995; (*c*) K. Ekoue-Kovi and C. Wolf, *Chem.–Eur. J.*, 2008, **14**, 6302–6315.
12 (*a*) C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790–792; (*b*) L. U. Nordstrom, H. Vogt and R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672–17673; (*c*) C. Chen, Y. Zhang and S. H. Hong, *J. Org. Chem.*, 2011, **76**, 10005–10010.
13 (*a*) W. K. Chan, C. M. Ho, M. K. Wong and C. M. Che, *J. Am. Chem. Soc.*, 2006, **128**, 14796–14797; (*b*) J. H. Park, S. Y. Kim, S. M. Kim and Y. K. Chung, *Org. Lett.*, 2007, **9**, 2465–2468; (*c*) X. Y. Mak, R. P. Ciccolini, J. M. Robinson, J. W. Tester and R. L. Danheiser, *J. Org. Chem.*, 2009, **74**, 9381–9387; (*d*) W. Wei, X.-Y. Hu, X.-W. Yan, Q. Zhang, M. Cheng and J.-X. Ji, *Chem. Commun.*, 2012, **48**, 305–307.
14 H. Chen, M. M. He, Y. Y. Wang, L. H. Zhai, Y. B. Cui, Y. Y. Li, Y. Li, H. B. Zhou, X. C. Hong and Z. X. Deng, *Green Chem.*, 2011, **13**, 2723–2726.
15 K. S. Goh and C. H. Tan, *RSC Adv.*, 2012, **2**, 5536–5538.
16 F. H. Xiao, Y. Liu, C. L. Tang and G. J. Deng, *Org. Lett.*, 2012, **14**, 984–987.
17 (*a*) H. Wolff, *Org. React.*, 1946, **3**, 307–336; (*b*) P. A. S. Smith, *Mol. Rearrange.*, 1963, **1**, 457–591; (*c*) G. I. Koldobskii, G. F. Tereshchenko, E. S. Gerasimova and L. I. Bagal, *Usp. Khim.*, 1971, **40**, 1790–1813.
18 (*a*) J. Aube and G. L. Milligan, *J. Am. Chem. Soc.*, 1991, **113**, 8965–8966; (*b*) V. Gracias, G. L. Milligan and J. Aube, *J. Am. Chem. Soc.*, 1995, **117**, 8047–8048; (*c*) G. L. Milligan, C. J. Mossman and J. Aube, *J. Am. Chem. Soc.*, 1995, **117**, 10449–10459; (*d*) V. Gracias, K. E. Frank, G. L. Milligan and J. Aube, *Tetrahedron*, 1997, **53**, 16241–16252; (*e*) K. Sahasrabudhe, V. Gracias, K. Furness, B. T. Smith, C. E. Katz, D. S. Reddy and J. Aube, *J. Am. Chem. Soc.*, 2003, **125**, 7914–7922; (*f*) L. Yao and J. Aube, *J. Am. Chem. Soc.*, 2007, **129**, 2766–2767.
19 (*a*) J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.*, 1955, **77**, 951–954; (*b*) J. H. Boyer, F. C. Canter, J. Hamer and R. K. Putney, *J. Am. Chem. Soc.*, 1956, **78**, 325–327; (*c*) R. Chakraborty, V. Franz, G. Bez, D. Vasadia, C. Popuri and C. G. Zhao, *Org. Lett.*, 2005, **7**, 4145–4148; (*d*) H. L. Lee and J. Aube, *Tetrahedron*, 2007, **63**, 9007–9015.
20 S. Ratti, P. Quarato, C. Casagrande, R. Fumagalli and A. Corsini, *Eur. J. Pharmacol.*, 1998, **355**, 77–83.
21 K. M. Belyk, H. G. Morrison, P. Jones and V. Summa, *Application WO Pat.*, WO 2006060712, 2006.
22 (*a*) K. J. French, Y. Zhuang, L. W. Maines, P. Gao, W. Wang, V. Beljanski, J. J. Upson, C. L. Green, S. N. Keller and C. D. Smith, *J. Pharmacol. Exp. Ther.*, 2010, **333**, 129–139; (*b*) J. A. McIntyre, J. Castaner and L. Martin, *Drugs Future*, 2004, **29**, 992–997; (*c*) G. A. Molander and M. A. Hiebel, *Org. Lett.*, 2010, **12**, 4876–4879.