Fast Assembly of 1*H*-Imidazo[1,2-*a*]imidazol-5-amines via Groebke–Blackburn–Bienaymé Reaction with 2-Aminoimidazoles

Olga P. Pereshivko,[1] Vsevolod A. Peshkov,[1] Denis S. Ermolat'ev, Erik V. Van der Eycken*

Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, 3001 Leuven, Belgium
Fax +32(16)327990; E-mail: erik.vandereycken@chem.kuleuven.be

Received: 30.09.2012; Accepted after revision: 14.12.2012

Abstract: A novel microwave-assisted protocol allowing the successful application of 2-aminoimidazoles in the Groebke–Blackburn–Bienaymé reaction for the facile construction of the 1*H*-imidazo[1,2-*a*]imidazol-5-amine core was developed.

Key words: multicomponent reactions, annulation, heterocycles, fused-ring systems

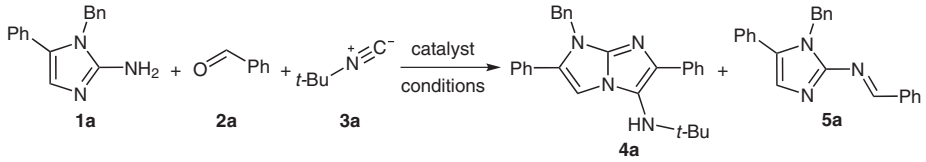
Isocyanide-based multicomponent reactions have been shown to be an efficient and operationally simple tool for the generation of great structural complexity and diversity.[2] The three-component Passerini and four-component Ugi reactions are probably the most attractive, owning to their exceptionally broad scope, functional group tolerance and the possibility of performing a variety of post-condensation transformations.[3] The three-component Groebke–Blackburn–Bienaymé variation of the Ugi reaction involves the Lewis or Brønsted acid catalyzed condensation of a 2-aminoazine or 2-aminoazole with an aldehyde and an isocyanide. Since its independent discovery by three research groups in 1998,[4] the Groebke–Blackburn–Bienaymé reaction has been established as a general approach to a wide range of azine- and azole-fused aminoimidazoles.[5,6] In a continuation of our long-standing interest in the chemistry of polysubstituted 2-aminoimidazoles[7,8] we were keen to explore them as substrates in this process because, to the best of our knowledge, only 2-aminobenzoimidazoles have been studied so far.[9]

We started our investigation with a model reaction of 1-benzyl-5-phenyl-1*H*-imidazol-2-amine (**1a**) with benzaldehyde (**2a**) and *tert*-butyl isocyanide (**3a**; Table 1). Typically Groebke–Blackburn–Bienaymé reactions are conducted in a polar protic solvent such as methanol. However, carrying out our model reaction in methanol with 5 mol% $HClO_4$ at room temperature for 24 hours[4c] generated only 7% of imine **5a** and no desired 1*H*-imidazo[1,2-*a*]imidazol-5-amine product **4a** could be detected (Table 1, entry 1). Analogous reactions carried out under microwave irradiation at 80 °C for 30 min also yielded only small quantities of imine **5a** (Table 1, entry 2). Switching to 10 mol% [$Yb(OTf)_3$] as catalyst improved the yield of imine **5a** but again no traces of **4a** were formed (Table 1, entry 3). Finally, elevating the reaction temperature to 110 °C allowed the desired product **4a** to be obtained in only 12% yield together with 50% yield of imine **5a** (Table 1, entry 4). A considerable improvement in the reaction outcome was achieved when switching to the nonpolar solvent toluene;[10] under these conditions, 1*H*-Imidazo[1,2-*a*]imidazol-5-amine **4a** was obtained in 48% yield (46% isolated yield) together with only 15% of the undesired imine **5a** (Table 1, entry 5). A further change of the parameters of the [$Yb(OTf)_3$]-catalyzed reaction or the use of [$Sc(OTf)_3$] did not provide any substantial improvement of the **4a** yield (Table 1, entries 6–10). We then turned our attention to the application of *p*-toluenesulfonic acid (TsOH), which has already been efficiently employed by several groups in the Groebke–Blackburn–Bienaymé reaction.[11] Carrying out the model reaction with 10 mol% $TsOH \cdot H_2O$ in toluene at 110 °C under microwave irradiation gave the desired 1*H*-imidazo[1,2-*a*]imidazol-5-amine **4a** in a good isolated yield of 52% (Table 1, entry 11). Further screening (Table 1, entries 12 and 13) revealed that the best catalyst loading was 20 mol%, which allows **4a** to be obtained in an improved yield of 69%. It is also important to stress that reactions run under conventional heating resulted in rather poor yields of **4a** even after an extended reaction time of 24 hours (Table 1, entries 14 and 15).

With these results at hand, we decided to evaluate the scope and limitations of our procedure (Table 2).[12,13] We tested various 1,5-disubstituted 2-aminoimidazoles **1a**–**k** in combination with benzaldehyde (**2a**) and *tert*-butyl isocyanide (**3a**). Running reactions under the developed optimal conditions (Table 1, entry 11) with some minor workup variations[13] we were able to obtain 1*H*-imidazo[1,2-*a*]imidazol-5-amines **4a**–**k** in reasonable yields ranging from 17 to 69% (Table 2, entries 1–11). We then screened several aromatic aldehydes **2b**–**f** in combination with **1a** and **3a** (Table 2, entries 12–16). The application of aldehydes bearing electron-withdrawing substituents in the aromatic ring gave the best results, allowing the isolation of the desired 1*H*-imidazo[1,2-*a*]imidazol-5-amines **4n**–**p** in very good yields ranging from 73 to 77% (Table 2, entries 14–16). Heteroaromatic picolinaldehyde (**2g**) and aliphatic butyraldehyde (**2h)** were also found to be applicable, delivering the expected products **4p** and **4q** in good yields of 41 and 54%, respectively (Table 2, entries 17 and 18). Carrying out the reactions with 1,1,3,3-tetra-

SYNLETT 2013, 24, 0351–0354
Advanced online publication: 16.01.2013
DOI: 10.1055/s-0032-1317986; Art ID: ST-2012-B0834-L

Table 1 Optimal Parameters for the Synthesis of 1*H*-Imidazo[1,2-*a*]imidazol-5-amine **4a**[a]



Entry	Catalyst (mol%)	Conditions				Yield (%)[b]	
						4a	**5a**
		Solvent	Time (min)	Temp (°C)	Heating method		
1	$HClO_4$ (5)	MeOH	24 h	25	conventional	0	7[c]
2	$HClO_4$ (5)	MeOH	30	80	MW	0	28[c]
3	$Yb(OTf)_3$ (10)	MeOH	30	80	MW	0	55[c]
4	$Yb(OTf)_3$ (10)	MeOH	30	110	MW	12	50
5	$Yb(OTf)_3$ (10)	toluene	30	110	MW	48, 46[d]	15
6	$Yb(OTf)_3$ (10)	toluene	30	80	MW	6	68
7	$Yb(OTf)_3$ (10)	toluene	30	130	MW	44	17
8	$Yb(OTf)_3$ (20)	toluene	30	110	MW	43	13
9	$Yb(OTf)_3$ (10 + 10)	toluene	25 + 15	110	MW	47	11
10	$Sc(OTf)_3$ (10)	toluene	30	110	MW	45[d]	–[e]
11	$TsOH·H_2O$ (10)	toluene	30	110	MW	52[d]	–[e]
12	**$TsOH·H_2O$ (20)**	**toluene**	**30**	**110**	**MW**	**69**[d]	–[e]
13	$TsOH·H_2O$ (30)	toluene	30	110	MW	62[d]	–[e]
14	$Yb(OTf)_3$ (10)	toluene	24 h	110	conventional	22	24
15	$TsOH·H_2O$ (20)	toluene	24 h	110	conventional	26[f]	25[f]

[a] All reactions were carried out on a 0.3 mmol scale with **1a**/**2a**/**3a** ratio = 1:1.2:1.5.
[b] Unless otherwise specified, yields were calculated from the ^{1}H NMR spectra of mixtures of **4a** and **5a** obtained directly by flash chromatography of the reaction mixture with no aqueous workup.
[c] Isolated yield obtained directly by flash chromatography of the reaction mixture with no aqueous workup.
[d] Isolated yield after the aqueous workup and flash chromatography.
[e] Not determined (**5a** decomposed in the presence of 1 M HCl during the aqueous workup).
[f] Yield determined by ^{1}H NMR spectroscopic analysis of the reaction mixture using 3,4,5-trimethoxybenzaldehyde as internal standard.

methylbutyl isocyanide (**3b**) provided products **4r** and **4s** in slightly diminished yields compared to the analogous reactions with *tert*-butyl isocyanide (**3a**; Table 2, entries 19 and 20 vs 1 and 7).

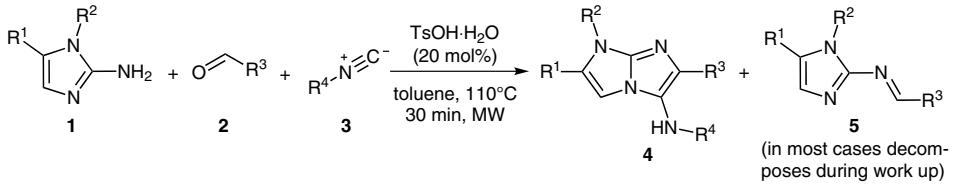
Cyclohexyl isocyanide (**3c**) applied in combination with **1a** and **2a** delivered 1*H*-imidazo[1,2-*a*]imidazol-5-amine **4t** in a relatively poor yield of 29% (Table 2, entry 21).

Unfortunately we were unable to isolate any significant amount of product from reactions conducted with **1a** and **2a** used in a combination with other isocyanides such as benzyl isocyanide (**3d**) or aromatic 2-naphthyl isocyanide (**3e**; Figure 1).

Another identified limitation is that, except for 1,5-disubstituted 2-aminoimidazoles, no other substitution pattern could be successfully applied in our protocol (Figure 1). This fact could probably be ascribed to the steric hindrance exerted by the substituent at the 4-position of the 2-aminoimidazole core during the ring-closure step (Figure 1).

In conclusion, we have developed a novel microwave-assisted protocol for the Groebke–Blackburn–Bienaymé reaction optimized specifically for the use of 1,5-disubstituted 2-aminoimidazoles, giving an access to 1*H*-imidazo[1,2-*a*]imidazol-5-amines. The scope and limitations of the process were studied by employing various aldehydes, isocyanides and 2-aminoimidazoles. A small library of 1*H*-imidazo[1,2-*a*]imidazol-5-amines having four points of diversity was prepared with yields ranging from 17 to 77%.

Table 2 Scope of the Groebke–Blackburn–Bienaymé Protocol[a]



Entry	R^1, R^2 (**1**)	R^3 (**2**)	R^4 (**3**)	**4**	Yield (%)[b]
1	Ph, Bn (**1a**)	Ph (**2a**)	*t*-Bu (**3a**)	**4a**	69
2	Ph, piperonyl (**1b**)	Ph (**2a**)	*t*-Bu (**3a**)	**4b**	35
3	Ph, 2-$BrC_6H_4CH_2$ (**1c**)	Ph (**2a**)	*t*-Bu (**3a**)	**4c**	31
4	Ph, 3,4-$(MeO)_2C_6H_3CH_2$ (**1d**)	Ph (**2a**)	*t*-Bu (**3a**)	**4d**	26
5	Ph, cyclohexyl (**1e**)	Ph (**2a**)	*t*-Bu (**3a**)	**4e**	18
6	Ph, cyclododecyl (**1f**)	Ph (**2a**)	*t*-Bu (**3a**)	**4f**	17
7	4-ClC_6H_4, cyclopropyl (**1g**)	Ph (**2a**)	*t*-Bu (**3a**)	**4g**	49
8	4-ClC_6H_4, Me (**1h**)	Ph (**2a**)	*t*-Bu (**3a**)	**4h**	36
9	4-ClC_6H_4, Bn (**1i**)	Ph (**2a**)	*t*-Bu (**3a**)	**4i**	24
10	4-PhC_6H_4, cyclobutyl (**1j**)	Ph (**2a**)	*t*-Bu (**3a**)	**4j**	36
11	4-$MeSC_6H_4$, Me (**1k**)	Ph (**2a**)	*t*-Bu (**3a**)	**4k**	27
12	Ph, Bn (**1a**)	4-MeC_6H_4 (**2b**)	*t*-Bu (**3a**)	**4l**	45
13	Ph, Bn (**1a**)	4-FC_6H_4 (**2c**)	*t*-Bu (**3a**)	**4m**	54
14	Ph, Bn (**1a**)	4-$F_3CC_6H_4$ (**2d**)	*t*-Bu (**3a**)	**4n**	73
15	Ph, Bn (**1a**)	4-NCC_6H_4 (**2e**)	*t*-Bu (**3a**)	**4o**	75
16	Ph, Bn (**1a**)	4-$O_2NC_6H_4$ (**2f**)	*t*-Bu (**3a**)	**4p**	77
17	Ph, Bn (**1a**)	pyridin-2-yl (**2g**)	*t*-Bu (**3a**)	**4q**	41
18	Ph, Bn (**1a**)	Pr (**2h**)	*t*-Bu (**3a**)	**4r**	54
19	Ph, Bn (**1a**)	Ph (**2a**)	1,1,3,3-tetramethylbutyl (**3b**)	**4s**	45
20	4-ClC_6H_4, cyclopropyl (**1g**)	Ph (**2a**)	1,1,3,3-tetramethylbutyl (**3b**)	**4t**	39
21	Ph, Bn (**1a**)	Ph (**2a**)	cyclohexyl (**3c**)	**4u**	29

[a] All reactions were carried out on a 0.3 mmol scale with **1a**/**2a**/**3a** ratio = 1:1.2:1.5.
[b] Isolated yield.

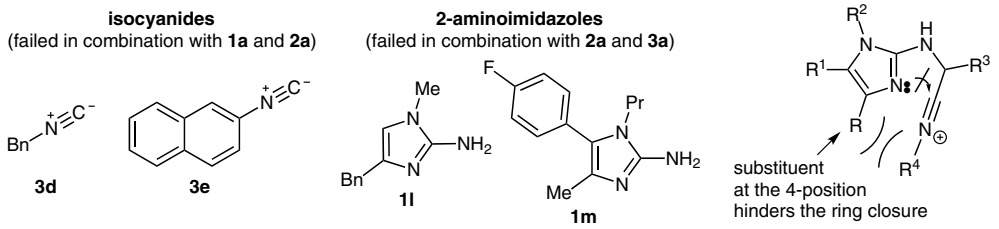


Figure 1 Unsuccessful substrates

Acknowledgment

Support was provided by the Fund for Scientific Research (FWO), Flanders and by the Research Fund of the University of Leuven (KU Leuven). V.A.P. is grateful to the EMECW (Triple I) for a doctoral scholarship. D.S.E. is grateful to the Fund for Scientific Research (FWO), Flanders for a postdoctoral fellowship. The authors thank Ir. B. Demarsin for valuable help with HRMS.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) The authors contributed equally to this work.

(2) For selected reviews covering different aspects of isocyanide-based multicomponent reactions, see: (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) De Moliner, F.; Banfi, L.; Riva, R.; Basso, A. *Comb. Chem. High Throughput Screening* **2011**, *14*, 782. (d) Elders, N.; Ruijter, E.; Nenajdenko, V. G.; Orru, R. V. A. *Top. Heterocycl. Chem.* **2010**, *23*, 129. (e) van Berkel, S. S.; Bögels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2012**, 3543. (f) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153. (g) Ivachtchenko, A. V.; Ivanenkov, Ya. A.; Kysil, V. M.; Krasavin, M.; Ilyin, A. P. *Russ. Chem. Rev.* **2010**, *79*, 787.

(3) For selected reviews on post-condensation transformations, see: (a) Banfi, L.; Basso, A.; Riva, R. *Top. Heterocycl. Chem.* **2010**, *23*, 1. (b) Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23.

(4) (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661. (b) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635. (c) Bienaymé, H.; Bouzid, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2234.

(5) For selected examples, see: (a) Krasavin, M.; Tsirulnikov, S.; Nikulnikov, M.; Kysil, V.; Ivachtchenko, A. *Tetrahedron Lett.* **2008**, *49*, 5241. (b) Guchhait, S. K.; Madaan, C. *Tetrahedron Lett.* **2011**, *52*, 56. (c) Lyon, M. A.; Kercher, T. S. *Org. Lett.* **2004**, *6*, 4989. (d) Schwerkooke, J.; Masquelin, T.; Perun, T.; Hulme, C. *Tetrahedron Lett.* **2005**, *46*, 8355. (e) Parchinsky, V. Z.; Koleda, V. V.; Schuvalova, O.; Kravchenko, D. V.; Krasavin, M. *Tetrahedron Lett.* **2006**, *47*, 6891. (f) Sandulenko, Y.; Komarov, A.; Rufanov, K.; Krasavin, M. *Tetrahedron Lett.* **2008**, *49*, 5990. (g) Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett.* **2007**, *48*, 4079. (h) Lamberth, C. *Synlett* **2011**, 1740. (i) Sharma, A.; Li, H.-y. *Synlett* **2011**, 1407. (j) Guasconi, M.; Lu, X.; Massarotti, A.; Caldarelli, A.; Ciraolo, E.; Tron, G. C.; Hirsch, E.; Sorba, G.; Pirali, T. *Org. Biomol. Chem.* **2011**, *9*, 4144.

(6) In some literature reports, the formation of two isomeric azine-fused aminoimidazole products was described, see: (a) Mandair, G. S.; Light, M.; Russell, A.; Hursthouse, M.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 4267. (b) Nenadjenko, V. G.; Reznichenko, A. L.; Balenkova, E. S. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 560. (c) Guchhait, S. K.; Madaan, C. *Synlett* **2009**, 628.

(7) For our advancements in the synthesis of polysubstituted 2-aminoimidazole derivatives, see: (a) Ermolat'ev, D. S.; Babaev, E. V.; Van der Eycken, E. V. *Org. Lett.* **2006**, *8*, 5781. (b) Ermolat'ev, D. S.; Alifanov, V. L.; Rybakov, V. B.; Babaev, E. V.; Van der Eycken, E. V. *Synthesis* **2008**, 2083. (c) Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Org. Chem.* **2008**, *73*, 6691. (d) Ermolat'ev, D. S.; Svidritzky, E. P.; Babaev, E. V.; Van der Eycken, E. *Tetrahedron Lett.* **2009**, *50*, 5218. (e) Steenackers, H. P. L.; Ermolat'ev, D. S.; Savaliya, B.; De Weerdt, A.; De Coster, D.; Shah, A.; Van der Eycken, E. V.; De Vos, D. E.; Vanderleyden, J.; De Keersmaecker, S. C. J. *J. Med. Chem.* **2011**, *54*, 472. (f) Ermolat'ev, D. S.; Bariwal, J. B.; Steenackers, H. P. L.; De Keersmaecker, S. C. J.; Van der Eycken, E. V. *Angew. Chem. Int. Ed.* **2010**, *49*, 9465. (g) Pereshivko, O. P.; Peshkov, V. A.; Ermolat'ev, D. S.; Van Hove, S.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Synthesis* **2011**, 1587.

(8) For our advancements in the elaboration of the 2-aminoimidazole core, see: Modha, S. G.; Mehta, V. P.; Ermolat'ev, D. S.; Balzarini, J.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. *Mol. Diversity* **2010**, *14*, 767.

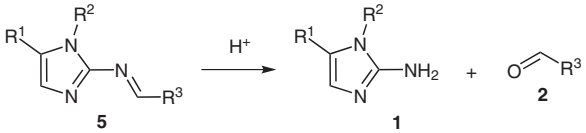
(9) Guchhait, S. K.; Madaan, C.; Thakkar, B. S. *Synthesis* **2009**, 3293.

(10) Parchinsky, V. Z.; Shuvalova, O.; Ushakova, O.; Kravchenko, D. V.; Krasavin, M. *Tetrahedron Lett.* **2006**, *47*, 947.

(11) (a) Mironov, M. A.; Tokareva, M. I.; Ivantsova, M. N.; Mokrushin, V. S. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 1835. (b) Rahmati, A.; Kouzehrash, M. A. *Synthesis* **2011**, 2913.

(12) **Microwave-Assisted Groebke–Blackburn–Bienaymé Reaction; Typical Procedure for 1-Benzyl-*N*-*tert*-butyl-2,6-diphenyl-1*H*-imidazo[1,2-*a*]imidazol-5-amine (4a):** To a microwave vial equipped with a magnetic stir bar containing **1a** (75 mg, 0.3 mmol) and *p*-toluenesulfonic acid hydrate (11 mg, 0.06 mmol), anhydrous toluene (1 mL), **2a** (38 mg, 0.36 mmol) and **3a** (37 mg, 0.45 mmol) were consecutively added. The reaction vessel was sealed and irradiated in the cavity of a CEM-Discover microwave reactor at a set temperature of 110 °C for 30 min. Upon completion of the reaction, the vial was cooled with a stream of air. The resulting reaction mixture was diluted with EtOAc (50 mL), thoroughly washed with 1 M HCl (2 × 50 mL) and sat. aq Na_2CO_3 (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was dissolved in EtOAc (5 mL) and subjected to flash chromatography [silica (25 g); EtOAc–heptane, 3:7] to give pure **4a** (87 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07–7.95 (m, 2 H), 7.41–7.26 (m, 7 H), 7.25–7.10 (m, 6 H), 6.94 (s, 1 H), 5.22 (s, 2 H), 2.90 (br s, 1 H), 1.12 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 145.5, 137.4, 136.3, 136.2, 133.3, 129.5, 128.9, 128.7, 128.62, 128.56, 128.47, 128.0, 127.4, 127.3, 126.0, 120.1, 102.5, 55.6, 47.0, 30.3; HRMS (EI): *m*/*z* calcd for $C_{28}H_{28}N_4$: 420.2314; found: 420.2281.

(13) CAUTION! The acidic aqueous workup was necessary in most cases to decompose imine **5**, which was otherwise difficult to separate from the desired product **4** (Scheme 1). See the Supporting Information for details.



Scheme 1

