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Bromodimethylsulfonium bromide (BDMS)-catalyzed multicomponent synthesis of 3-aminoalkylated indoles

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ABSTRACT

Bromodimethylsulfonium bromide (BDMS)-catalyzed three-component coupling reaction between indoles, aldehydes, and *N*-alkylanilines is reported to access substituted 3-aminoalkylated indoles at room temperature in high yields (82–96%) within 1.5–3.5 h. The salient features of this protocol are the simplicity of the procedure, the ready accessibility of the catalyst, its cost effectiveness, and higher yields in relatively short reaction times.

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, as high degrees of molecular diversity can be introduced by these reactions in a very fast, efficient, and time saving manner without the isolation of any intermediates.[1] As a result, considerable attention has been paid to the development of new and improved one-pot multicomponent reactions in recent years.[2] Besides this, the utility of MCRs is well represented in the synthesis of privileged medicinal scaffolds such as 1,4-dihydropyridines, dihydropyrimidines, decahydroquinolin-4-ones, and substituted indoles.[3,4]

3-Substituted indole moieties are of much importance as they are widely distributed in nature and reveal a broad range of biological activities.[5] Indoles with aminoalkyl/aryl substituents at the 3-position are considered as venerable pharmacophores[6] in drug discovery and are found in various natural products[7] such as 5-HT1B/1D with receptor agonist activities used in the treatment of migraine, aromatase inhibitor for breast cancer,[8] and HIV-1 integrase inhibitors[9] Gramine, Ergine, and Sumatriptant. The immense potential of indole nucleus as drug candidates prompted among the synthetic chemists to explore different methods suitable for the synthesis of 3-substituted indoles.

Despite several methods available in the literature for the synthesis of substituted indoles,[10] there are only a few reports on the access of substituted 3-aminoalkylated indoles using MCR protocols.[10d,i–l] It is thus evident that there remains a wide scope for the development of clean and efficient methodologies for the preparation of these derivatives through a convenient and environmentally friendly method. Herein, we report a convenient method for the synthesis of 3-aminoalkylated indoles via rapid three-component coupling reaction between indoles, aldehydes, and *N*-alkylanilines using bromodimethylsulfonium bromide (BDMS) as a catalyst as shown in Scheme 1.

Bromodimethylsulfonium bromide (BDMS),[11] a commercially available light orange solid compound, has gained considerable interest in organic synthesis after the discovery by Meerwein[11c] due to its easy handling, low cost, as well as its easy access, and varied applications both as a catalyst[12] and as an effective reagent.[13] In continuation of our recent work on the development of useful new synthetic methodologies using bromodimethylsulfonium bromide (BDMS)[14] we observed that the treatment of indoles with aldehydes and *N*-alkylanilines at room temperature in the presence of BDMS in ethanol afforded the corresponding 3-aminoalkylated indoles **1** (Scheme 1).

Initially, we investigated the multicomponent reaction of benzaldehyde, aniline, and indole in the presence of BDMS (10 mol %) as a catalyst. Unfortunately, the reaction did not proceed according to expectations. However, we were delighted to find that the reaction proceeded well when aniline was replaced with *N*-methylaniline. In the screening of different solvents to find the most suitable solvent for this transformation, ethanol was found to be superior to other solvents such as acetonitrile, THF, 1,4-dioxane, and DCM in terms of both reaction times and yields obtained (Table 1, entries 1–5). Attempts were also made to study this protocol with Lewis

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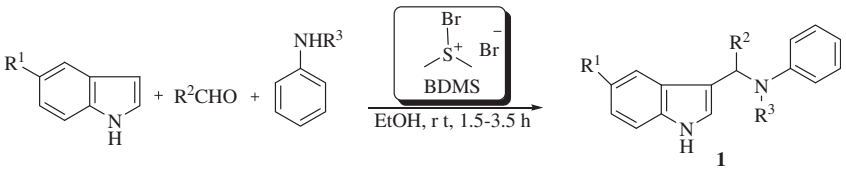


Scheme 1. Synthesis of 3-aminoalkylated indoles **1**.

Table 1
Optimization conditions for condensation of *N*-methylaniline, benzaldehyde, and indole[a]

Entry	Solvent[b]	Catalyst (mol %)	Time (h)	Yield[c] (%)
1	EtOH	BDMS (10)	2.5	96
2	CH_3CN	BDMS (10)	4	90
3	THF	BDMS (10)	4	40
4	1,4-Dioxane	BDMS (10)	4	40
5	DCM	BDMS (10)	4	50
6	EtOH	BDMS (20)	2.5	96
7	EtOH	BDMS (5)	4	80
8	EtOH	Boric acid (10)	2.5	20[d]
9	EtOH	$InCl_3$ (10)	2.5	24[d]
10	[Hmim]HSO_4	—	2.5	12[d]

[a] All reactions were performed using aldehyde 1 mmol, *N*-methylaniline, 2 mmol and indole 1 mmol. For experimental details, see Ref. 15.
[b] 1.0 mL was used.
[c] Yields are related to isolated pure products.
[d] Bis(indolyl)methane is the major product.

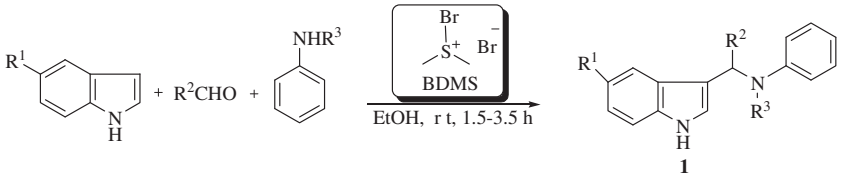
acids such as $InCl_3$, boric acid (10 mol % each), and protic ionic liquid [Hmim]HSO_4-both as solvent and catalyst, but bis(indolyl)methane was obtained as the major product (Table 1, entries 8–10).

The best catalytic activity of BDMS was optimized to be 10 mol % (Table 1, entry 1) and any excess catalyst, beyond this proportion (10 mol %), did not show further increase in the conversion and yield of the product (Table 1, entry 6) while decreasing the amount of catalyst from 10 to 5 mol % lowered the substrate conversion rate (Table 1, entry 7). The scope and generality of this method is illustrated with respect to different indoles, aldehydes, and *N*-alkylanilines and the results are summarized in Table 2.[15] The conversion was completed within 1.5–3.5 h and the product was formed in high yields 82–96%. 1*H*-Indole, 5-bromo-1*H*-indole, and 5-methoxy-1*H*-indole were employed as the indole derivatives, different aldehydes, including aromatic aldehydes with electron-donating and electron-withdrawing groups, and different *N*-alkylanilines such as *N*-methyl-, *N*-ethyl-, and *N*-propylanilines, afforded the desired products in high yields. *N*-Alkylanilines were used in excess to avoid the formation of bis(indolyl)alkanes. Various functional groups such as halogen, hydroxy, ether, and nitro groups remain intact. All the products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy.

A plausible mechanism for BDMS-catalyzed formation of 3-aminoalkylated indoles **1** is depicted in Scheme 2. *N*-alkylanilines react with aldehydes in the presence of BDMS to form an iminium ion intermediate along with Me_2SO. Iminium ion intermediate is then attacked by an electron rich indole to afford 3-aminoalkylated indoles **1** (Scheme 2) with elimination of HBr. The reaction between Me_2SO and HBr then regenerates BDMS to complete the catalytic cycle.

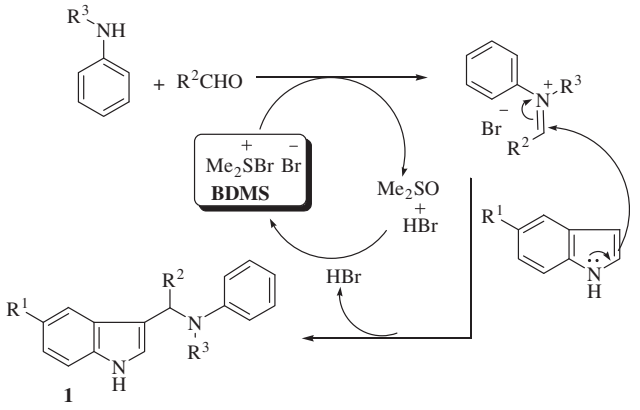
In summary, we have demonstrated the efficacy and generality of bromodimethylsulfonium bromide (BDMS) as a versatile catalyst for the synthesis of 3-aminoalkylated indoles via an efficient and rapid three-component coupling reaction between indoles, aldehydes, and *N*-alkylanilines at room temperature. The salient features of the present protocol are the simplicity of the procedure, the ready accessibility of the catalyst, and its cost effectiveness, higher yields in relatively short reaction times. Thus, this atom–

Table 2
BDMS-catalyzed multicomponent route to access substituted 3-aminoalkylated indoles **1**[a]



Entry	R1	R^2	R^3	Product[b]	Time (h)	Yield[c] (%)
1	H	C_6H_5	Me	**1a**	2.5	96
2	H	4-ClC_6H_4	Me	**1b**	2.0	89
3	H	4-$MeOC_6H_4$	Me	**1c**	3.0	84
4	H	4-MeC_6H_4	Me	**1d**	2.0	86
5	H	4-$O_2NC_6H_4$	Me	**1e**	1.5	94
6	H	C_6H_{11}	Me	**1f**	2.5	86
7	OMe	4-MeC_6H_4	Me	**1g**	2.0	91
8	OMe	4-ClC_6H_4	Me	**1h**	1.5	94
9	Br	4-$MeOC_6H_4$	Me	**1i**	3.0	85
10	Br	4-$O_2NC_6H_4$	Me	**1j**	2.0	88
11	H	3,4-$(MeO)_2C_6H_3$	Et	**1k**	3.5	82
12	H	4-$O_2NC_6H_4$	Et	**1l**	2.0	89
13	H	3,4-$(MeO)_2C_6H_3$	Pr	**1m**	3.5	85
14	H	4-HOC_6H_4	Pr	**1n**	3.0	84

[a] See Ref. 15 for general procedure.
[b] All the products are known compounds[10d,i] and were characterized by comparison of their mp and spectral data with those of authentic samples.
[c] Yields of pure isolated products after column chromatography.



Scheme 2. Plausible mechanistic illustration of BDMS-catalyzed formation of 3-aminoalkylated indoles **1**.

economic methodology would be a practical alternative to the existing protocols for the synthesis of such kind of fine chemicals.

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References and notes

1. (a) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. pp 1–32; (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (d) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957; (e) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321; (g) Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266.
2. (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965; (c) Ghosh, R.; Maiti, S.; Ghosh, S.; Mukherjee, A. K. *Synthesis* **2007**, 190; (d) Cui, S.-L.; Lin, X.-F.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 4517.
3. (a) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2002**, *67*, 6979; (b) Lin, C.; Fang, H.; Tu, Z.; Liu, J.-T.; Yao, C.-F. *J. Org. Chem.* **2006**, *71*, 6588; (c) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899; (d) Dardennes, E.; Kovacs-Kulyassa, A.; Boisbrun, M.; Petermann, C.; Laronze, J.-Y.; Sapi, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1329; (e) Dardennes, E.; Kovacs-Kulyassa, A.; Renzetti, A.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett.* **2003**, *44*, 221.
4. (a) Albright, J. D.; Snyder, H. R. *J. Am. Chem. Soc.* **1959**, *81*, 2239; (b) Biekert, E.; Funck, T. *Chem. Ber.* **1964**, *97*, 363; (c) Hogan, I.; Jenkins, P. D.; Sainsbury, M. *Tetrahedron* **1990**, *46*, 2943.
5. (a) Jiang, B.; Yang, C.-G.; Wang, J. *J. Org. Chem.* **2001**, *66*, 4865; (b) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083; (c) Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393; (d) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125.
6. (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996; (b) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
7. For reviews on indole containing natural products, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155; (b) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175.
8. (a) Leze, M.-P.; Le Borgne, M.; Marchand, P.; Loquet, D.; Kogler, M.; Le Baut, G.; Palusczak, A.; Hartmann, R. W. *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 549; (b) Le Borgne, M.; Marchand, P.; Delevoye-Seiller, B.; Robert, J.-M.; Le Baut, G.; Hartmann, R. W.; Palzer, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 333.
9. (a) Deng, J.; Sanchez, T.; Neamati, N.; Briggs, J. M. *J. Med. Chem.* **2006**, *49*, 1684; (b) Contractor, R.; Samudio, I. J.; Estrov, Z.; Harris, D.; McCubrey, J. A.; Safe, S. H.; Andreeff, M.; Konopleva, M. *Cancer Res.* **2005**, *65*, 2890.
10. (a) Wynne, J. H.; Stalick, W. M. *J. Org. Chem.* **2002**, *67*, 5850; (b) Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. *Adv. Synth. Catal.* **2003**, *345*, 557; (c) Ji, S.-J.; Wang, S.-Y.; Zhang, Y.; Loh, T.-P. *Tetrahedron* **2004**, *60*, 2051; (d) Srihari, P.; Sing, V. K.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *50*, 3763; (e) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 1621; (f) Renzetti, A.; Dardennes, E.; Fontana, A.; De Maria, P.; Sapi, J.; Gerand, S. *J. Org. Chem.* **2008**, *73*, 6824; (g) Kobayashi, K.; Shirai, Y.; Konishi, H. *Heterocycles* **2009**, *78*, 2033; (h) Fridkin, G.; Boutard, N.; Lubell, W. D. *J. Org. Chem.* **2009**, *74*, 5603; (i) Das, B.; Kumar, J. N.; Kumar, A. S.; Damodar, K. *Synthesis* **2010**, 914; (j) Sharifi, A.; Mirzaei, M.; Naimi-Jamal, M. R. *Monatsh. Chem.* **2001**, *132*, 875; (k) Dai, H.-G.; Li, J.-T.; Li, T. S. *Synth. Commun.* **2006**, *36*, 1829; (l) Zao, J.-L.; Liu, L.; Zhang, H.-B.; Wu, Y.-C.; Wang, D.; Chen, Y.-F. *Synlett* **2006**, 96.
11. (a) Choudhury, L. H.; Pravin, T.; Khan, A. T. *Tetrahedron* **2009**, *65*, 9513. and references cited therein; (b) Olah, G. A.; Vankar, Y. D.; Arvanaghi, M.; Surya Prakash, G. K. *Synthesis* **1979**, 720; (c) Meerwein, H.; Zenner, K. F.; Gipp, R. *Justus Liebigs Ann. Chem.* **1965**, *67*, 688; (d) Choudhury, L. H. *Synlett* **2006**, 1619; (e) Furukawa, N.; Inoue, T.; Aida, T.; Oae, S. *J. Chem. Soc., Chem. Commun.* **1973**, 212a.
12. (a) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Adv. Synth. Catal.* **2008**, *305*, 1696; (b) Khan, A. T.; Parvin, T.; Gazi, S.; Choudhury, L. H. *Tetrahedron Lett.* **2007**, *48*, 3805; (c) Khan, A. T.; Parvin, T.; Choudhury, L. H. *Eur. J. Org. Chem.* **2008**, 834; (d) Khan, A. T.; Parvin, T.; Choudhury, L. H. *J. Org. Chem.* **2008**, *73*, 8398; (e) Das, B.; Holla, H.; Srinivas, Y. *Tetrahedron Lett.* **2007**, *48*, 61.
13. (a) Das, B.; Srinivas, Y.; Sudhakar, C.; Ravikanth, B. *J. Chem. Res.* **2008**, 188; (b) Das, B.; Srinivas, Y.; Holla, H.; Laxminarayana, K.; Narender, R. *Tetrahedron Lett.* **2007**, *48*, 6681; (c) Jiang, B.; Dou, Y.; Xu, X.; Xu, M. *Org. Lett.* **2008**, *10*, 593.
14. (a) Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2009**, *50*, 5532; (b) Yadav, L. D. S.; Garima; Srivastava, V. P. *Tetrahedron Lett.* **2010**, *51*, 739; (c) Yadav, L. D. S.; Patel, R.; Srivastava, V. P. *Synthesis* **2010**, 1771.
15. *General procedure for the synthesis of 3-aminoalkylated indoles*: A mixture of aldehyde (1 mmol), *N*-alkylaniline (2 mmol) and, bromodimethylsulfonium bromide (BDMS) (10 mol %) in EtOH (1 mL) was stirred at rt for 30 min followed by addition of indole (1 mmol) and stirring is continued till the completion of the reaction as indicated by TLC (Table 2). The reaction mixture was diluted with water (15 mL) and extracted with ether (4 × 5 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude product was purified by column chromatography (silica gel, hexane–EtOAc) to obtain analytically pure indoles **1**. All the products are known compounds[10d,i] and were characterized by comparison of their mp and spectral data with those of authentic samples.