$Bi(OTf)_3$-Catalyzed Three-Component Synthesis of Amidomethylarenes and -Heteroarenes

Angelika E. Schneider, Georg Manolikakes*

Department of Organic Chemistry and Chemical Biology, Goethe University Frankfurt, Max-von-Laue-Straße 7, 60438 Frankfurt am Main, Germany
Fax +49(69)79829248; E-mail: g.manolikakes@chemie.uni-frankfurt.de

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Abstract: A highly efficient $Bi(OTf)_3$-catalyzed multicomponent synthesis of amidomethylated arenes and heteroarenes from readily available starting materials has been developed. This reaction proceeds under mild conditions, has a broad substrate scope, and in addition water is generated as only side product.

Key words: multicomponent reactions, bismuth, green chemistry, acylimines, amidoalkylation

Amidomethyl moieties, in particular amidomethylated arenes, are frequently found in biologically active molecules (Figure 1).[1]

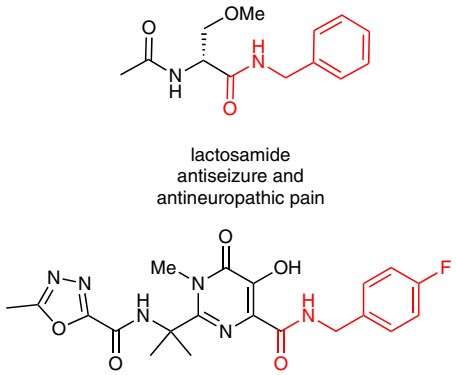
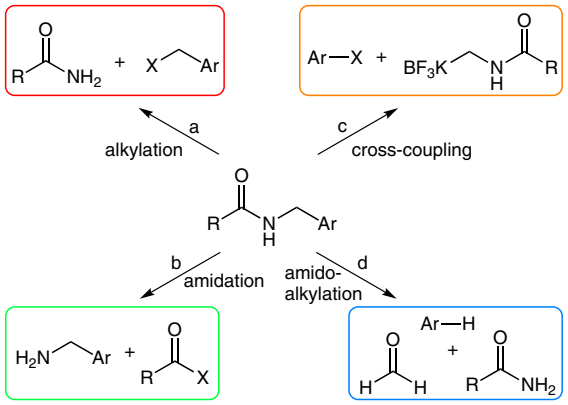


Figure 1 Amidomethyl moiety in biologically active molecules

Most commonly, these compounds are synthesized by N-alkylation of amides with benzylic halides[2] (Scheme 1, path a) or amide-bond forming reactions[3] (path b). Recently, Molander has developed a complementary route based on palladium-catalyzed cross-coupling reactions[4] (path c). However, a decisive disadvantage of all these methods is the utilization of prefunctionalized, often not readily available starting materials. Another disadvantage is the generation of stoichiometric amounts of waste.[5]

A different synthetic route is the Mannich-type amidoalkylation of arenes with acylimines or acyliminium ions.[6,7] Especially the in situ generation of these reactive imine derivatives from an aldehyde and an amide represents an atom-economical[8] synthesis of amidoalkylated (hetero)arenes (path d). Generating water as only side product, these reactions could meet the requirements of modern sustainable organic synthesis. However, all common procedures either employ preformed acylimine precursors or use stoichiometric amounts of Lewis or Brønsted acid.[9] Hence considerable amounts of waste are generated in these processes.



Scheme 1 Possible routes to amidomethylated arenes

Our interest in developing new multicomponent reactions for the rapid synthesis of pharmaceutically relevant molecules has led us to closer examination of these three-component amidoalkylation reactions. We envisioned, that by careful choice of the catalyst, the development of a truly catalytic and general three-component amidoalkylation should be possible. Herein, preliminary studies towards this goal are disclosed. Initially, we focused on the identification of a suitable catalyst using the reaction between benzamide (**1a**), paraformaldehyde (**2**), and *m*-xylene (**3a**), as moderately reactive arene, in dichloroethane (DCE) as model system (Table 1). From a multitude of tested Lewis and Brønsted acids only $Bi(OTf)_3$ efficiently catalyzed this transformation, furnishing the desired amidoalkylation product **4a** in 61% yield (Table 1, entry 2). Since $Bi(OTf)_3$ is commercially available, nontoxic, air- and moisture-stable, it is a very attractive catalyst.[10–12]

Other Bi^{3+} salts such as $BiCl_3$ and $BiBr_3$, as well as HOTf showed no comparable catalytic activity for this transformation (Table 1, entries 3–5). Performing the reaction in nitromethane as solvent led to an increased yield of 84% (Table 1, entry 6). By reducing the catalyst loading to 2.5 mol%, an 85% yield of the desired product was obtained

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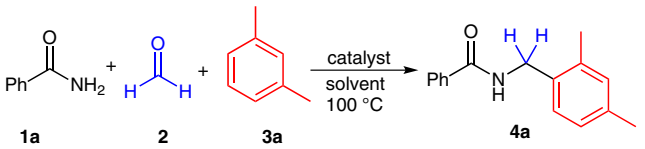
Table 1 Survey of Catalysts[a]



1a **2** **3a** **4a**

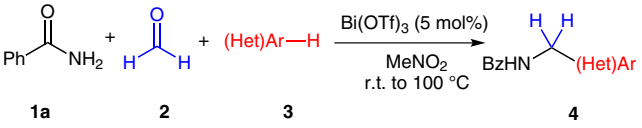
Entry	Catalyst (mol%)	Yield (%)[b]
1	$M(OTf)_x$ (5)[d] M = Cu, Zn, In, Sc, Mg, Yb	<5
2	$Bi(OTf)_3$ (5)[d]	61[c]
3	$BiBr_3$ (5)[d]	<5
4	$BiCl_3$ (5)[d]	<5
5	HOTf (5)[d]	10
6	$Bi(OTf)_3$ (5)[e]	84[c]
7	$Bi(OTf)_3$ (2.5)[e]	85[c]
8	$Bi(OTf)_3$ (5)[e,f]	79[c]
9	$Bi(OTf)_3$(5) + dbpy (10)[e]	75[c]

[a] General reaction conditions: benzamide (1.0 equiv), *p*-formaldehyde (1.2 equiv), *m*-xylene (3.0 equiv), catalyst (x mol%), 100 °C, 18 h.
[b] Isolated yield of analytical pure product.
[c] Obtained as a 15:1 mixture of regioisomers.
[d] Reaction in DCE.
[e] Reaction in $MeNO_2$.
[f] Reaction with aqueous formalin.

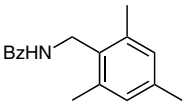
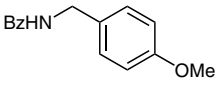
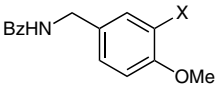
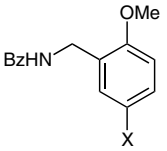
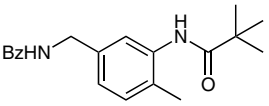
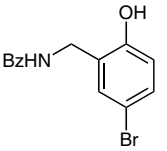
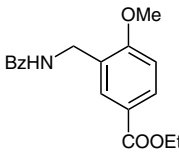
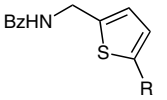
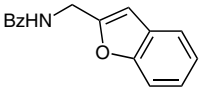
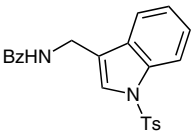
(Table 1, entry 7). It has to be emphasized that this reaction is quite insensitive to air and moisture and therefore very simple to perform. Switching from paraformaldehyde to an aqueous formalin solution as formaldehyde source gave the product **4a** in comparable 79% yield (Table 1, entry 8). Performing the reaction in the presence of the proton scavenger 2,6-di-*tert*-butylpyridine (dbpy)[13] did not led to a significant decrease in yield (Table 1, entry 8).

These results suggest that $Bi(OTf)_3$ is the active catalyst and no 'hidden Brønsted acid catalysis'[14] occurs. With the optimized conditions in hand, we investigated the scope of the reaction. Various electron-rich arenes, such as mesitylene (**3b**), anisole (**3c**), and its halogenated derivatives **3d–i** furnished the desired amidoalkylation products **4b–i** in good to excellent yields (Table 2, entries 1–8). In most cases, the reactions provide the amidomethylated arenes with high regioselectivity or as single regioisomer. Only in the case of anisole (**3c**) a 3:1 mixture of regioisomers is obtained. Unprotected phenols or acid-labile ester functionalities were well tolerated under the reaction conditions (Table 2, entries 10 and 11). The reaction with the sterically hindered pivaloyl amide **3j** proceeded chemoselectively and afforded the amidomethylarene **4j** in 66% yield (Table 2, entry 9). In the case of heteroarenes, lower reaction temperatures were required to avoid direct addition of the heteroarene to formaldehyde.[15] Several electron-rich heterocycles, such as different substituted thiophenes **3m–o**, benzofuran (**3p**), or *N*-tosylindole

Table 2 Variation of Arenes and Heteroarenes[a]



1a **2** **3** **4**

Entry	Product		Yield (%)[b]
1		**4b**	73[c]
2		**4c**	68 (3:1)[d]
3		**4d** X = Br	88[c]
4		**4e** X = Cl	84[c]
5		**4f** X = I	79[c]
6		**4g** X = Br	77[c]
7		**4h** X = Cl	83[c]
8		**4i** X = I	64[c]
9		**4j**	66[c]
10		**4k**	68[c]
11		**4l**	87[c]
12		**4m** R = Me	64 (12:1)[d,e]
13		**4n** R = Br	94[c]
14		**4o** R = Cl	69[c,e]
15		**4p**	70 (24:1)[d,e]
16		**4q**	76 (14:1)[d,e]

[a] General reaction conditions: benzamide (1.0 equiv), *p*-formaldehyde (1.2 equiv), *m*-xylene (3.0 equiv), $Bi(OTf)_3$ (5 mol%).
[b] Isolated yield of analytical pure product.
[c] Obtained as single regioisomer.
[d] Obtained as a mixture of regioisomers, ratio of regioisomers given in parentheses.
[e] Reaction with aqueous formalin.

(**3q**)[16] gave the corresponding amidomethylated products **4m–q** in 64–94% yield (Table 2, entries 12–16). For some of these heteroaromatics (**3m**,**o–q**) considerably higher

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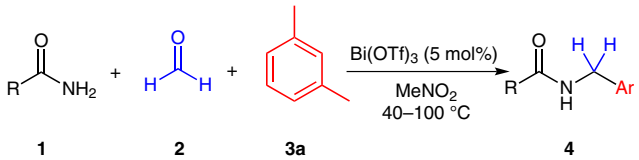
yields were obtained with aqueous formalin as formaldehyde source.

The scope of the reaction is not limited to benzamide as amide component. Reaction of paraformaldehyde and *m*-xylene with other primary aryl or alkyl amides furnished the desired amidoalkylation products **4r**–**x** in good to excellent yields and regioselectivities (Table 3, entries 1–7). Acid-sensitive functionalities, such as a cyano group or an acrylamide were well tolerated (Table 3, entries 6 and 7). Using carbamates as amide component, the corresponding N-protected aminomethyl arenes **4y** und **4z** were obtained in 71% and 45% yield (Table 3, entries 8 and 9). Therefore this method also provides straightforward access to aminomethylated arenes, which are found in various bioactive compounds.[17] Secondary amides did not react under our standard conditions, with the exception of the cyclic carbamate **1aa** (Table 3, entry 10).[18] Finally, reaction with the phthalimide-protected valinamide **1ab** provided the amino acid derivative **4ab** in 63% yield (Table 3, entry 11).

Table 3 Variation of Amides[a]



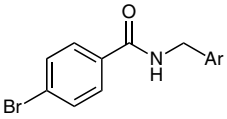
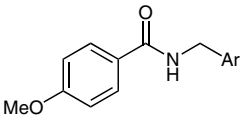
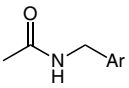
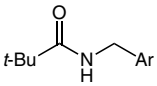
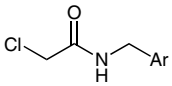
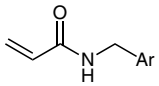
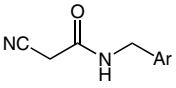
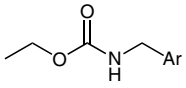
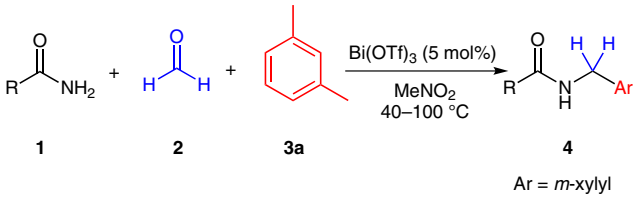
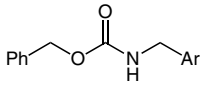
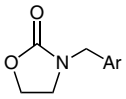
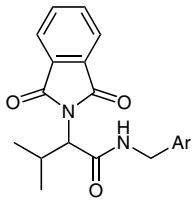
Entry	Product		Yield (%)[b]
1		**4r**	70 (24:1)[d]
2		**4s**	65[c]
3		**4t**	51 (15:1)[d]
4		**4u**	77 (17:1)[d]
5		**4v**	73 (18:1)[d]
6		**4w**	55 (13:1)[d]
7		**4x**	96 (11:1)[d]
8		**4y**	71[c]

Table 3 Variation of Amides[a] (continued)



Entry	Product		Yield (%)[b]
9		**4z**	45 (14:1)[d]
10		**4aa**	71[c] (>25:1)
11		**4ab**	63 (12:1)[c,d]

[a] General reaction conditions: benzamide (1.0 equiv), *p*-formaldehyde (1.2 equiv), *m*-xylene (3.0 equiv), $Bi(OTf)_3$ (5 mol%).
[b] Isolated yield of analytical pure product.
[c] Obtained as single regioisomer.
[d] Obtained as a mixture of regioisomers, ratio of regioisomers given in parentheses.

In summary we have developed an efficient $Bi(OTf)_3$-catalyzed three-component reaction between amides, formaldehyde, and arenes.[19] This practical and operational simple method provides straightforward and versatile access to amidomethylated arenes or heteroarenes. The scope of the reaction is quite broad and water is generated as only side product. Using carbamates as amide component different protected amidomethylarenes could be synthesized. Studies to expand the scope of this method and to investigate the reaction mechanism are currently under way in our laboratory.

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

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(10) Reviews: (a) Bothwell, J. M.; Krabbe, S. W.; Mohan, R. S. *Chem. Soc. Rev.* **2011**, *40*, 4649. (b) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517.

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(15) See Supporting Information for experimental details.

(16) Reactions with indoles not bearing electron-withdrawing N-protecting groups or other more reactive heterocycles such as furan or pyrrole led to the exclusive formation of bisheteroarylmethane derivatives.

(17) (a) Musher, D. M.; Fainstein, V.; Young, E. J. *Antimicrob. Agents Chemother.* **1980**, 254. (b) Campoli-Richards, D.; Lackner, T.; Monk, J. *Drug* **1987**, *34*, 411. (c) Kaczanowska, K.; Wiesmuller, K.-H.; Schaffner, A.-P. *ACS Med. Chem. Lett.* **2010**, *1*, 530.

(18) This might be due to the decreased sterical shielding of **4ab**.

(19) **Typical Procedure**
A 10 mL screw-cap vial was charged with $Bi(OTf)_3$ (5 mol%), amide (1.0 equiv), formaldehyde (1.2 equiv), (hetero)arene (3–4 equiv), and nitromethane and closed with a Teflon lined screw cap. The reaction mixture was stirred at 25–100 °C for the specified time. After cooling to r.t. the reaction mixture was diluted with EtOAc and filtered over a short plug of Celite and silica gel. The plug was rinsed with additional EtOAc. The combined filtrates were concentrated under reduced pressure. Purification of the crude residue by column chromatography (hexane–EtOAc) afforded the analytically pure product.
Synthesis of *N*-(2,4,6-Trimethylbenzyl)benzamide (4b, Table 2 Entry 1)
N-(2,4,6-Trimethylbenzyl)benzamide was synthesized according to the typical procedure from benzamide (242 mg, 2.0 mmol), paraformaldehyde (72 mg, 2.4 mmol), mesitylene (0.83 mL, 6.0 mmol, 3 equiv), and $Bi(OTf)_3$ (66 mg, 0.1 mmol) in $MeNO_2$ (4 mL) at 100 °C for 16 h. Purification by chromatography (hexane–EtOAc, 4:1) yielded the product as colorless solid (371 mg, 73%).

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