A Comparative Study of Groebke-Blackburn-Bienaymé Reactions Catalyzed by M(OTf)3 under Microwave Heating

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Abstract

Herein, we present a comparative study of Groebke-Blackburn-Bienaymé reactions catalyzed by $M(OTf)_3$ (M = Sc, La, Gd, Eu, La, Y, Yb, In and Bi) under microwave heating which furnished imidazopyridines as products in good to excellent yields.

Introduction

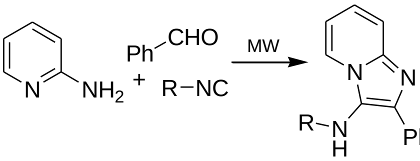
Multicomponent reactions (MCRs) are processes involving three or more starting materials combining together in a single step to afford a product with high atom efficiency.[1] 1H-Imidazo[1,2-a]pyridine moiety is present in several compounds with important biological activities such as Alpidem® (anxiolytic) and Zolpidem® (hypnotic). This scaffold is easily accessed *via* the Groebke-Blackburn-Bienaymé reaction (GBB) between an isocyanide, an aldehyde and an amidine.[2] So far, several different protocols for GBB MCR have been published elsewhere, most of them employing acid catalysts and common solvents under reflux for prolonged reaction times.[1d,e] In this work we describe our results on the investigation of such reaction catalyzed by different metal triflates under microwave heating.

Results & Discussion

Firstly, we selected two model reactions to be studied. Then, 2-aminopyridine, benzaldehyde, *tert*-butylisocyanide or methyl isocyanoacetate and 5 mol% of the catalyst were dissolved in MeOH and heated at 150°C for 30 minutes in a microwave sealed vial (Table 1).

The use of $Sc(OTf)_3$ in GBB reactions are very common, despite the fact that no systematic study on the use of this catalyst under microwave heating was reported until now. In our hands, reactions using 5 mol% of $Sc(OTf)_3$ led to **1** and **2** in 76% and 98% yield, respectively (entries 1 and 10). Uncatalyzed reaction led to the product **2** in only 13% yield (entry 9). Then, we carried out a screening of different metal triflates in order to find cheaper alternatives to more expensive $Sc(OTf)_3$. For instance, the yields obtained for **2** with cheaper $Gd(OTf)_3$ and $La(OTf)_3$ were 90% in both cases (entries 11 and 12). In general, the yields were quite similar with those obtained for **1** and **2** when $Sc(OTf)_3$ was used (entries 1-8 and 10-17).

Table 1. $M(OTf)_3$-catayzed GBB reactions under microwave heating.



1 R = CH_2CO_2Me
2 R = $C(CH_3)_3$

Entry	Catalyst	Product	Yield
1	$Sc(OTf)_3$	**1**	76%
2	$Gd(OTf)_3$	**1**	69%
3	$La(OTf)_3$	**1**	49%
4	$Y(OTf)_3$	**1**	62%
5	$Yb(OTf)_3$	**1**	65%
6	$Eu(OTf)_3$	**1**	68%
7	$Bi(OTf)_3$	**1**	65%
8	$In(OTf)_3$	**1**	70%
9	No catalyst	**2**	13%
10	$Sc(OTf)_3$	**2**	98%
11	$Gd(OTf)_3$	**2**	90%
12	$La(OTf)_3$	**2**	90%
13	$Y(OTf)_3$	**2**	60%
14	$Yb(OTf)_3$	**2**	73%
15	$Eu(OTf)_3$	**2**	72%
16	$Bi(OTf)_3$	**2**	83%
17	$In(OTf)_3$	**2**	82%

Reagents & Conditions: 2-Aminopyridine (1.0 mmol), benzaldehyde (1.0 mmol), *tert*-butylisocyanide or methyl isocyanoacetate (1.0 mmol) in MeOH (3.0 mL) and 5 mol% of $M(OTf)_3$ were stirred at 150°C for 30 minutes under microwave heating in a sealed tube (Anton Paar Microwave 300).

Conclusions

In this comparative study, we showed that cheap metal triflates catalysts such as $La(OTf)_3$ or $Gd(OTf)_3$ can be reasonable alternatives for $Sc(OTf)_3$ in Groebke-Blackburn-Bienaymé reactions carried out under microwave heating. The extension of this protocol to new nitrogen heterocycles with different substitution pattern is undergoing in our laboratory.

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[1] For some recent reviews on MCR and GBB reactions see: (a) Brauch, S.; van Berkela, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948; (b) Liu, Z.Q. *Curr. Org. Synth.* **2015**, *12*, 20; (c) Cioc, R. C.; Rujter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958; (d) Bagdi, A. K.; Santra, S.; Monir, L.; Hajra, A. *Chem. Commun.* **2015**, *51*, 1555; (e) Pericherla, K.; Kaswan, P.; Pandey, K.; Kumar, A. *Synthesis* **2015**, *47*, 887.

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