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Rare-earth metal triflates catalyzed three-component coupling of aldehydes, ketones or ketoesters and benzyl carbamate: An efficient one-pot stereoselective synthesis of Cbz-protected β-amino carbonyl compounds☆

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Abstract

$Sc(OTf)_3$ and $Yb(OTf)_3$ have been found to be efficient catalysts for one-pot three-component coupling of aldehydes, ketones or ketoesters and benzyl carbamate in acetonitrile at room temperature to furnish the corresponding Cbz-protected β-amino ketones in impressive yields and good diastereoselectivity.

Keywords: $Sc(OTf)_3$; $Yb(OTf)_3$; Cbz-protected β-amino ketone; Three-component coupling; Diastereoselectivity

1. Introduction

β-Amino carbonyl compounds are useful synthetic precursors of various pharmaceuticals and natural products [1,2]. They can be converted into amino alcohols which are utilized for the synthesis of antibiotics [3]. Recently two methods have been developed for three-component reactions of aldehydes, ketones and carbamates using $AuCl_3$–PPh_3 [4] and iodine [5] to form the corresponding Cbz-protected β-amino ketones. Carbamates can easily be deprotected [6]. So these products can be converted into β-amino ketones or can be utilized for other modifications keeping the amine group undisturbed. However, $AuCl_3$ is expensive and 5 equiv. of the ketone and 1.5 equiv. of the carbamate were required to treat 1 equiv. of aldehyde. The second catalyst, iodine, conducts the conversion in longer time.

2. Experimental

Acetophenone, propiophenone, ethyl acetoacetate, benzyl carbamate and all aromatic aldehydes were purchased from Aldrich or Fluka and used without further purification. $Sc(OTf)_3$ and $Yb(OTf)_3$ were purchased From Aldrich. ACME silica gel (60–120 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F_{254} plates. All other solvents and chemicals were obtained from commercial sources and purified using standard methods.

2.1. General procedure for the synthesis of Cbz-protected β-amino ketones

To a solution of $Sc(OTf)_3$ (10 mol%) in MeCN (3 ml) was added the aldehyde (1 mmol), propiophenone (1.5 mmol) and benzyl carbamate (1 mmol). The reaction mixture was stirred vigorously at room temperature with a magnetic stirrer during the mentioned time (Table 1). The reaction mixture was filtered and the filtrate was concentrated. Water (10 ml) was added to the residue and the mixture was extracted with ether (3× 5 ml). The extract was concentrated and the viscous mass was subjected to column chromatography (silica gel, 6% EtOAc in hexane) to obtain pure Cbz-protected β-amino carbonyl compound.

The spectral (^{1}H and ^{13}C NMR and MS) data of some representative products are given below.

3g: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (2H, d, J = 8.0 Hz), 7.34 (2H, d, J = 8.0 Hz), 7.32–7.21 (5H, m), 7.20 (2H, d,

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$J = 8.0$ Hz), 7.07 (2H, d, $J = 8.0$ Hz), 5.82 (1H, brs), 5.22 (1H, m), 5.02 (2H, s), 3.62 (1H, dd, $J = 12.0$, 4.0 Hz), 3.28 (1H, dd, $J = 12.0$, 6.0 Hz), 2.59 (2H, q, $J = 7.0$ Hz), 1.18 (3H, t, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 197.2, 156.7, 144.1, 138.7, 136.4, 135.0, 129.7, 129.1, 128.3, 127.5, 126.1, 65.8, 51.4, 28.8, 15.0; FABMS: m/z 424, 422 $[M+H]^+$.

3j: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.24 (2H, d, $J = 8.0$ Hz), 8.02 (2H, d, $J = 8.0$ Hz), 7.37–7.22 (5H, m), 7.20 (2H, d, $J = 8.0$ Hz), 7.11 (2H, d, $J = 8.0$ Hz), 5.58 (1H, brs), 5.21 (1H, m), 5.04 (2H, s), 3.77 (1H, dd, $J = 12.0$, 4.0 Hz), 3.39 (1H, dd, $J = 12.0$, 6.0 Hz), 2.60 (2H, q, $J = 7.0$ Hz), 1.22 (3H, t, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 196.4, 155.7, 150.2, 144.6, 141.8, 135.5, 129.1, 128.2, 127.5, 127.0, 126.3, 124.1, 65.4, 51.2, 28.2, 28.1, 14.9; FABMS: m/z 433 $[M+H]^+$.

3l (*syn*): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72 (2H, d, $J = 8.0$ Hz), 7.47 (1H, t, $J = 8.0$ Hz), 7.40–7.22 (7H, m), 7.15 (2H, d, $J = 8.0$ Hz), 7.01 (2H, d, $J = 8.0$ Hz), 6.54 (1H, d, $J = 8.5$ Hz), 5.08 (2H, s), 5.01 (1H, dd, $J = 8.4$, 4.2 Hz), 4.01 (1H, m), 2.53 (2H, q, $J = 7.0$ Hz), 1.32 (3H, d, $J = 7.0$ Hz), 1.12 (3H, t, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 204.6, 156.1, 143.8, 139.1, 137.0, 133.8, 129.7, 129.5, 128.2, 126.6, 65.5, 44.9, 28.3, 16.2, 15.1; FABMS: m/z 390 $[M+H]^+$.

3l (*anti*): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (2H, d, $J = 8.0$ Hz), 7.51 (1H, t, $J = 8.0$ Hz), 7.42 (2H, t, $J = 8.0$ Hz), 7.35–7.22 (5H, m), 7.19 (2H, d, $J = 8.0$ Hz), 7.09 (2H, d, $J = 8.0$ Hz), 5.16 (1H, d, $J = 8.6$ Hz), 5.11 (1H, t, $J = 8.5$ Hz), 5.06 (1H, d, $J = 12.0$ Hz), 4.99 (1H, t, $J = 12.0$ Hz), 3.97 (1H, m), 2.59 (2H, q, $J = 7.0$ Hz), 1.23 (3H, d, $J = 7.0$ Hz), 1.14 (3H, t, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 201.8, 155.6, 144.1, 138.3, 136.4, 133.2, 129.1, 129.0, 127.9, 126.2, 66.2, 45.1, 28.0, 15.1, 13.8; FABMS: m/z 390 $[M+H]^+$.

3. Result and discussion

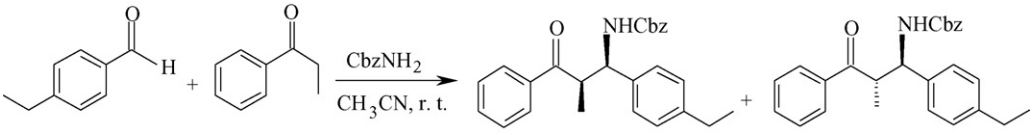
As a part of our on-going interest for development of useful synthetic methodologies [7,8] we have discovered that the rare earth metal triflates, $Sc(OTf)_3$ and $Yb(OTf)_3$ can catalyze efficiently the three-component coupling reaction of aromatic aldehydes, ketones or ketoesters and benzyl carbamate in MeCN at room temperature to generate Cbz-protected β-amino ketones (Scheme 1).

$Sc(OTf)_3$ and $Yb(OTf)_3$ are of great interest in recent years for their unique reactivities and selectivities under mild reaction conditions [9,10]. They are stable and work as a water compatible Lewis acids. So the anhydrous conditions of the reactions are not needed. In the present conversion 10 mol% of the catalyst was found to be highly effective for the preparation of Cbz-protected β-amino ketones.

Various aromatic aldehydes and acetophenones (or propiophenone or β-ketoesters) were utilized to prepare a series of products. Initially, the three-component reaction of 4-ethyl benzaldehyde, propiophenone and $CbzNH_2$ was examined at room temperature using several homogeneous and heterogeneous catalysts (Table 1) as well as different solvents such as CH_2Cl_2, MeCN, MeOH, THF, toluene and water. $Sc(OTf)_3$ as well as $Yb(OTf)_3$ (10 mol%) was found to be the best catalyst in MeCN to afford the desired Cbz-protected β-amino ketone in high yield and high diastereoselectivity. The catalytic activity of both $Sc(OTf)_3$ and $Yb(OTf)_3$ was found to be almost similar with a little variation of diastereoselectivity. Furthermore, the result was more impressive when a mixture of 4-ethyl benzaldehyde (1 mmol), propiophenone (1.5 mmol) and $CbzNH_2$ (1 mmol) was used.

Following our developed standard protocol a variety of aromatic aldehydes and acetophenone were treated with $CbzNH_2$

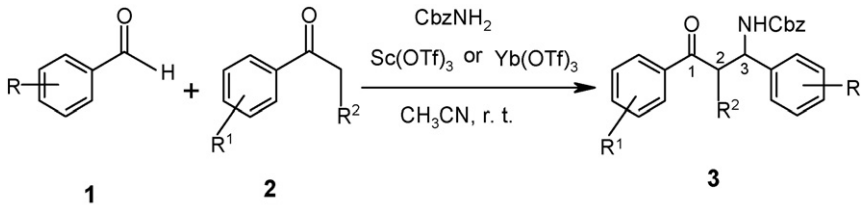
Table 1
Synthesis of Cbz-protected β-amino ketones using different heterogeneous and homogeneous catalysts



syn *anti*

Entry	Catalyst	Amount of catalyst (mol%)	Time (h)	Yield (%)	Selectivity (*syn*:*anti*)
1	$Sc(OTf)_3$	5	12	72	16:84
		10	8	92	10:90
2	$Yb(OTf)_3$	5	12	68	21:79
		10	8	92	12:88
3	Amberlyst-15	50[a]	12	64	–
		100[a]	12	73	30:70
4	$InCl_3$	10	12	43	–
5	KSF-Clay	50[a]	12	N.R.	–
6	Mont-K-10	50[a]	12	N.R.	–
7	$NaHSO_4$–SiO_2	50[a]	12	15	–
8	$HClO_4$–SiO_2	50[a]	12	22	–
9	CAN	20	12	N.R.	–

[a] Catalyst was taken in mg.

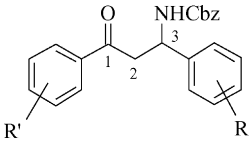
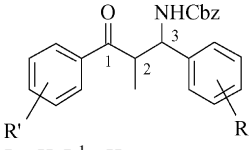
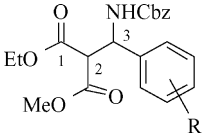


Scheme 1.

in the presence of 10 mol% of $Sc(OTf)_3$ (Table 1). The aldehydes containing electron-donating group in the aromatic ring underwent the conversion smoothly while 4-nitro benzaldehyde did not afford any product. However, acetophenones having electron-donating and electron-withdrawing groups yielded the desired products equally.

The reactions of aromatic aldehydes, propiophenone and benzyl carbamate in the presence of $Sc(OTf)_3$ were diastereoselective leading to the formation of *anti*-diastereoisomer as the major product (Table 2). Both the diastereoisomers were separated by column chromatography. The diastereoselectivity was determined from the ^{1}H NMR spectral data and by comparison of the values with those reported earlier [11–13]. In the ^{1}H NMR spectrum of a Cbz-protected β-amino ketone the coupling constant of H-2 and H-3 is 7–9 Hz for an *anti*-isomer while 2–5 Hz for a *syn*-isomer. These data were useful to establish the structures of both diastereoisomers.

Table 2
$Sc(OTf)_3$ catalyzed synthesis of Cbz-protected β-amino ketones[a]

Entry	Cbz-protected β-amino ketone (**3**)	Time (h)	Isolated yield (%)	*syn*:*anti*
				
a	R = H, R^1 = H	8	89	–
b	R = 4-Et, R^1 = H	8	93	–
c	R = 4-Me, R^1 = H	8	90	–
d	R = 4-OMe, R^1 = H	8	74	–
e	R = 4-Cl, R^1 = H	10	87	–
f	R = H, R^1 = 4-Cl	8	73	–
g	R = 4-Et, R^1 = 4-Cl	8	71	–
h	R = H, R^1 = 4-Br	8	77	–
i	R = 4-Et, R^1 = 4-Br	8.5	88	–
j	R = 4-Et, R^1 = 4-NO_2	8	84	–
				
k	R = H, R^1 = H	8	90	13:87
l	R = 4-Et, R^1 = H	8	92	10:90
m	R = 4-Cl, R^1 = H	10	87	14:86
n	R = 4-OMe, R^1 = H	8.5	83	20:80
o	R = 4-NO_2, R^1 = H	12	–	–
p	R = 2-NO_2, R^1 = H	12	–	–
				
q	R = H	7.5	78	45:55
r	R = 4-Et	8	83	40:60
s	R = 4-Cl	10	75	46:54
t	R = 4-NO_2	12	–	–
u	R = 2-NO_2	12	–	–

[a] The structures of the products were settled from spectral (^{1}H and ^{13}C NMR and MS) data.

The present conversion was also examined with aromatic aldehydes, ethyl acetoacetate and benzyl carbamate under the similar reaction conditions (Table 2). The yields of the products were high but diastereoselectivity was not impressive.

4. Conclusion

In conclusion, we have demonstrated a mild and efficient protocol for the diastereoselective high-yielding synthesis of Cbz-protected β-amino carbonyl compounds using three-component coupling reactions of aromatic aldehydes, ketones or ketoesters and $CbzNH_2$ in the presence of $Sc(OTf)_3$ or $Yb(OTf)_3$ as a catalyst.

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