One-pot Efficient Synthesis of Cbz-protected β-Amino Ketones: Three-component Coupling of Aldehydes, Ketones, and Benzyl Carbamate[1]

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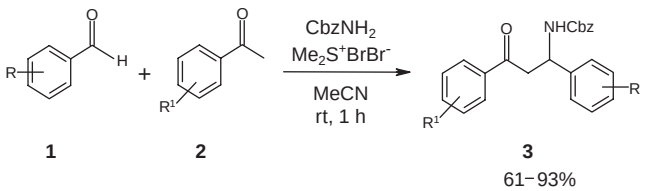
An efficient one-pot three-component reactions of aldehydes, ketones, and benzyl carbamate in the presence of a catalytic amount of (bromodimethyl)sulfonium bromide have been accomplished in short reaction time to afford the corresponding Cbz-protected β-amino ketones in high yields and good diastereoselectivity.

Multicomponent coupling reactions[2] (MCRs) have emerged as useful tools for the carbon–carbon bond-forming reactions and for accessing small drug-like molecules with several degrees of structural diversity. These reactions are widely utilized for constructing β-amino carbonyl compounds which are important synthetic intermediates for various pharmaceuticals and natural products.[3] Recently, Xu et al.[4] and Phukan et al.[5] reported two procedures for a three component reaction of aldehydes, ketones, and carbamates for the preparation of Cbz-protected β-amino ketones using $AuCl_3$–PPh_3 and Iodine respectively. However, the metal salt is expensive and 5 equiv. of the ketones and 1.5 equiv. of the carbamates are treated with 1 equiv. of the aldehydes. On the other hand, with iodine long conversion time is required. Here, we describe an efficient method for the synthesis of Cbz-protected β-amino ketones using bromodimethylsulfonium bromide as a catalyst.

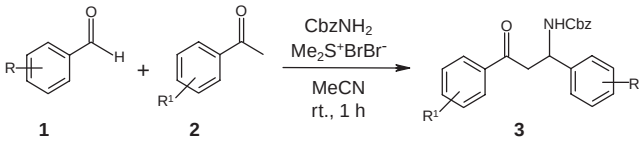
In continuation of our work[6] on the development of useful synthetic methodologies, we describe here for the first time the application of bromodimethylsulfonium bromide[7] to catalyze the reactions of aldehydes, ketones, and benzyl carbamate to generate Cbz-protected β-amino ketones in acetonitrile at room temperature (Scheme 1). Carbamates can be deprotected easily[8] and thus this method is an easy access to the β-amino carbonyl compounds. Cbz-protected β-amino ketones can also directly be applied for structural modifications without effecting the amine group.

A variety of aromatic aldehydes and acetophenone derivatives were tested using our method (Table 1). The reaction with aromatic aldehydes containing electron-donating groups afforded the corresponding Cbz-protected β-amino ketones in good to excellent yields (61–93%). The conversion was complete in 1 h. The best result was obtained when the ratio of aldehyde, ketone, and benzyl carbamate was 1.0:1.5:1.0. However, with 4-nitrobenzaldehyde the aldol product was formed in high yield.



Scheme 1.

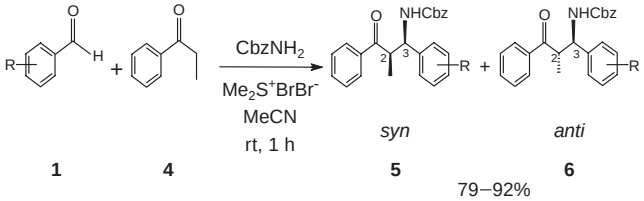
Table 1. Reaction of aldehydes and ketones with $CbzNH_2$ in acetonitrile at room temperature[a]



Entry	R	R^1	Isolated yield /%
A	H	H	89
B	4-Et	H	93
C	4-Me	H	90
D	4-OMe	H	74
E	4-Cl	H	87
F	H	4-Cl	73
G	4-Et	4-Cl	71
H	4-Me	4-Cl	69
I	4-Cl	4-Cl	83
J	H	4-Br	77
K	4-Et	4-Br	88
L	4-Cl	4-Br	61
M	4-NO_2	H	—
N	4-Et	4-NO_2	84

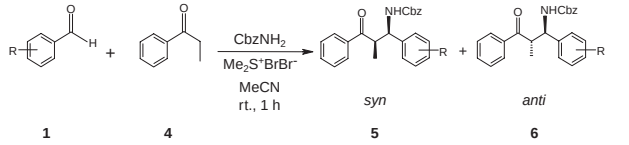
[a]The structure of the products were established from spectral (^{1}H and ^{13}C NMR and MS) data. Compounds **3b**, **3g**, **3k**, and **3n** are new.

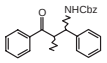
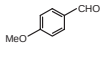
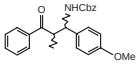
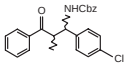
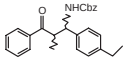
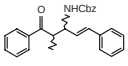
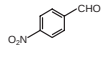
The reactions of aromatic aldehydes, benzyl carbamate, and propiophenone were diastereoselective leading to the formation of anti diastereomers as the major products (Scheme 2, Table 2). As for an example, from the reaction of 4-ethylbenzaldehyde and propiophenone (Entry D) the anti diastereomer was isolated by column chromatography as a major product (90% of the isolated yield) along with a minor amount (10% of the isolated yield) of syn diastereomer. Generally good diastereoselective Cbz-protected β-amino ketones were obtained from a variety of aldehydes. The diastereoselectivity was determined from the ^{1}H NMR spectral data (the coupling constant between H-2 and H-3 for an anti isomer is 7–9 Hz while for a syn isomer 3–5 Hz) and by comparison of the values reported in the literature.[9,10]



Scheme 2.

Table 2. Diastereoselective synthesis of Cbz-protected β-amino ketones[a]



Entry	Aldehyde	Ketone	Product (**5** and **6**)	Isolated yield/%	Selectivity syn:anti (**5**:**6**)
A				90	13:87
B				92	10:90
C				87	14:86
D				82	19:81
E				79	30:70
F			—	—	—
G			—	—	—

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

The yields of the products derived from aromatic aldehydes containing electron-donating groups were impressive. However, 4-nitrobenzaldehyde and 2-nitrobenzaldehyde afforded aldol products in high yields. In the case of aliphatic aldehydes such as propanal and hexanal complex mixtures of unidentified products were formed while cinnamaldehyde (Entry E) furnished the desired product in good yield (79%).

In conclusion, this note describes an efficient procedure for the synthesis of Cbz-protected β-amino carbonyl compounds with the use of bromodimethylsulfonium bromide catalyzed three-component coupling reactions involving aldehydes, ketones, and $CbzNH_2$ in acetonitrile medium at room temperature. The methodology described here is a distinct improvement over other previous protocols in terms of enhanced yields and good diastereoselectivity along with the advantages of mild reaction conditions, application of an inexpensive catalyst and low catalyst loading (10 mol %). The method is a convenient access to β-amino carbonyl compounds. Cbz-protected β-amino ketones can also be utilized for direct chemical modifications without disturbing the amine group.

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References and Notes

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10 Supporting Information is available on the CSJ-Journal web site; http://www.csj.jp/journals/chem-lett/index.html.

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