Pergamon

Tetrahedron Letters 43 (2002) 3891–3894

TETRAHEDRON LETTERS

Convenient synthesis of Cbz-protected β-amino ketones by a copper-catalysed conjugate addition reaction

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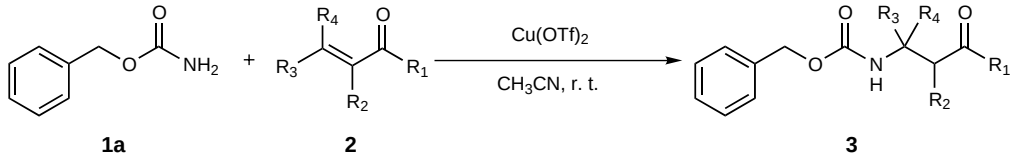
Received 29 March 2002; accepted 2 April 2002

Abstract—A convenient synthesis of Cbz-protected β-amino ketones is reported. Benzyl carbamates and α,β-unsaturated ketones furnish the conjugate addition products in the presence of a Cu(II) catalyst under mild conditions. Other weakly basic nitrogen nucleophiles can also be used in this reaction.

The synthesis of β-amino carbonyl compounds continues to attract attention due to the importance of this structural motif in organic chemistry. For example, β-amino acids occur in nature both in their free form and in peptides. Various synthetic β-amino acids show interesting pharmacological properties and serve as precursors in the synthesis of β-lactams, an important class of antibiotics.[1] Similarly, β-amino ketones are important intermediates in the synthesis of natural products and antibiotics. They are also useful precursors for the generation of β-amino alcohols, which are common reagents in the preparation of fine chemicals and pharmaceuticals.[2]

The classical method for the synthesis of β-amino ketones is the Mannich reaction of methyl ketones, amines and paraformaldehyde. Although recent advances have made this route more attractive, Mannich reactions often suffer from the drawbacks of long reaction times and harsh reaction conditions, which impair the applicability in the synthesis of complex molecules.[3] Another common route to β-amino ketones is the amine alkylation of β-haloketones, but owing to simplicity and atom economy, the more widely used method is the conjugate addition of nitrogen nucleophiles to α,β-unsaturated enones.[4] A large number of nucleophiles have been used in this reaction. Some reactive alkyl and aryl amines can be added to C–C multiple bonds without further activation, but with other nitrogen sources it is normally necessary to perform the reaction in the presence of acid[5] or base[6] catalysts. To circumvent disadvantages associated with the use of such additives, considerable effort has been spent towards the development of alternative methods. Apart from the novel sequential substitution/conjugate addition methodology of Gomtsyan[7] and the aziridino alcohol rearrangement by Tu,[8] these efforts have so far been focussed on Lewis acid mediated conjugate addition processes. Very recently an efficient catalytic version employing $CeCl_3$–NaI has been developed by the Bartoli group.[9] However, most methods for intermolecular conjugate addition to unsaturated ketones reported to date describe the addition of alkyl or aryl amines, which may be difficult to transform into other amino compounds in the course of a multistep synthesis.

We recently reported the conjugate addition of benzyl carbamate to α,β-unsaturated enones catalysed by cationic palladium complexes,[10] leading to β-amino



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

Scheme 1. Copper-catalysed addition of benzyl carbamate to α,β-unsaturated ketones.

Keywords: benzyl carbamate; conjugate addition; nitrogen nucleophiles; copper; β-amino ketones.

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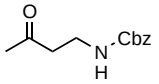
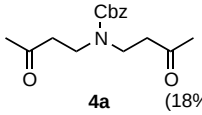
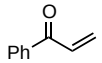
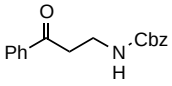
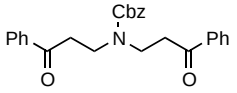
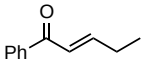
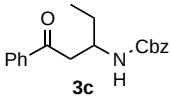
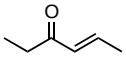
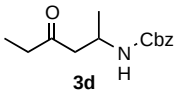
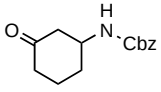
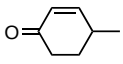
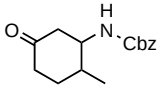
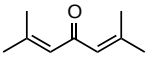
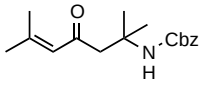
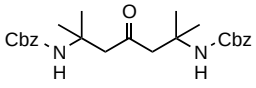
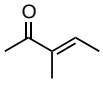
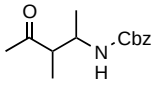
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00654-8

ketones bearing a benzyloxycarbonyl (Cbz) moiety which can easily undergo further conversions using well-established protective group chemistry.[11] During our ongoing investigations of the scope and the mechanism of this process, we discovered that the palladium catalyst could be substituted by much cheaper copper compounds. We wish to report our results on a very mild and highly efficient copper-catalysed conjugate addition reaction of unactivated benzyl carbamate and related nucleophiles to α,β-unsaturated ketones (Scheme 1).

A variety of copper(II) compounds, such as $CuCl_2$, $Cu(SbF_6)_2$[12] or Woodward's copper carbene complex,[13] could be used in this transformation. The highest reaction rates were observed with commercially available $Cu(OTf)_2$, which was superior to the palladium catalysts in terms of turnover frequency. Copper(I) complexes did not catalyse the reaction at all, nor, surprisingly, did typical Lewis acid catalysts such as $Ni(ClO_4)_2$ or $Yb(OTf)_3$ which have been found to be effective in related conjugate addition reactions.[14] The best results were obtained when a 0.7 M solution of the unsaturated ketone, 10% of the copper catalyst and 1.5 equiv. of benzyl carbamate (**1a**) in acetonitrile was stirred at room temperature. Conveniently, the reaction could be performed in commercially available analytical grade solvents and inert atmosphere conditions were not necessary.

A range of simple α,β-unsaturated ketones were screened and the results are summarised in Table 1. The efficiency of the transformation was found to be strongly dependent on the structure of the acceptor molecule. Terminal enones were highly reactive and apart from the desired compounds diaddition products

Table 1. Conjugate addition of benzyl carbamate (**1a**) to α,β-unsaturated ketones

entry[a]	α,β-enone	time	product	yield[%][b]	byproducts[b]
1	 **2a**	4 h	 **3a**	81	 **4a** (18%)
2	 **2b**	12 h	 **3b**	53	 **4b** (37%)
3	 **2c**	3 h	 **3c**	99	-
4	 **2d**	1 h	 **3d**	81	-
5[c]	 **2e**	12 h	 **3e**	87	-
6[c]	 **2f**	12 h	 **3f**[d]	75	-
7	 **2g**	48 h	 **3g**	47	 **4g** (16%)
8	 **2h**	12 h	 **3h**[e]	28	-
9	 **2i**	48 h	no reaction	-	-

[a]Benzyl carbamate **1a** (1.5 mmol) was added to a solution of **2** (1.0 mmol) and $Cu(OTf)_2$ (0.1 mmol) in CH_3CN (1.5 ml) and stirred at room temperature. [b]Isolated yields after column chromatography. [c]At -35 °C to avoid decomposition. [d]d.r. 6:1. [e]d.r. 10:1.

could be isolated (entries 1, 2). Good to excellent yields of the β-amino ketones were obtained with disubstituted internal enones (entries 3–6). In analogy to the palladium-catalysed process reported earlier, substituents other than a proton on the α-carbon of the acceptor molecule led to a dramatic loss of reactivity (entries 8, 9). Although **3h** could only be isolated in modest yield, a high diastereomeric ratio was observed. Good diastereocontrol was also observed when the γ-substituted cyclohexenone **2f** was used (entry 6). The reaction was thermodynamically controlled in some cases with the equilibrium position determining the maximum yield. Unreacted starting materials could be reisolated.

To explore the effect of placing additional steric demands on the nitrogen nucleophile, the alkylated carbamates **1b**–**1d** were employed in the addition reaction (Table 2). It was found that these reagents still gave good yields with methylvinylketone (**2a**) (entries 1–3), but when **2c** was used as an acceptor, a pronounced decrease in yield was observed with increasing steric congestion (entries 4–6). This observation also explains why the expected cyclisation product was not detected in earlier experiments with the dienone **2g**; instead, products arising from single and double addition to the acceptor were isolated (entry 7, Table 1).

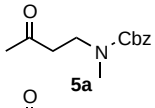
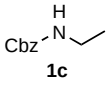
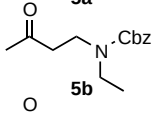
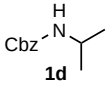
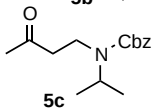
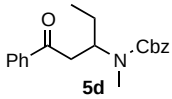
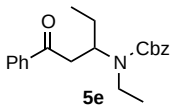
For further exploration of the structural types of nucleophiles which can be used in this reaction, we turned our attention towards the use of other unactivated, non- or only weakly basic nitrogen sources (Table 3). We were pleased to find that fluorenylmethyl carbamate (**6a**) gave excellent yield in the addition reaction, but due to the low solubility of **6a** in acetonitrile long reaction times were necessary (entry 1). The hydroxylamine **6d** reacted readily with **2c** to give the desired adduct **7d** in moderate yield in addition to the intramolecular cyclisation product **8d** (entry 4). The oxazolidinone **6b** and benzaldehyde oxime (**6c**) were also effective nucleophiles and furnished the addition products in good yields (entries 2, 3), confirming our initial assumption that weakly basic nitrogen sources are particularly suited for this reaction, as they do not bind too strongly to the transition-metal catalyst.

In conclusion, we have demonstrated that Cbz-protected β-amino ketones can be prepared selectively in a simple, $Cu(OTf)_2$-catalysed conjugate addition reaction under very mild conditions. Apart from experimental simplicity, the advantages of this methodology are the use of a cheap catalyst and the insensitivity of the reaction mixture towards air and moisture. We are currently investigating the development of an enantioselective catalytic process and the use of chiral nitrogen nucleophiles as well as acceptor molecules other than α,β-unsaturated ketones. Our results will be reported in due course.

Experimental

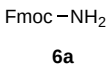
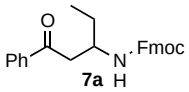
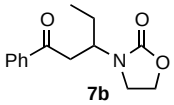
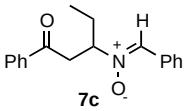
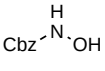
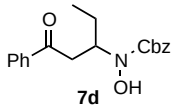
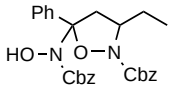
Representative experimental procedure as used in the preparation of **3c**: Copper(II) triflate (36 mg, 0.1 mmol) and the ketone **2c** (160 mg, 1.0 mmol) were dissolved in acetonitrile (1.5 ml). Benzyl carbamate (**1a**) (227 mg, 1.5 mmol) was added. The light blue solution was stirred at room temperature and conversion was monitored by TLC. After the starting material had been consumed, the reaction mixture was adsorbed onto silica gel and the product was isolated by column chromatography (eluting solvent ether/petrol ether 3:1). Yield: 307 mg (99%). ^{1}H NMR (400 MHz, $CDCl_3$)

Table 2. Effect of alkyl substituents at the carbamate nitrogen atom

entry[a]	nucleophile	α,β-enone	time	product	yield[%][b]
1	 **1b**	**2a**	24 h	 **5a**	83
2	 **1c**	**2a**	48 h	 **5b**	74
3	 **1d**	**2a**	48 h	 **5c**	63
4	**1b**	**2c**	24 h	 **5d**	71
5	**1c**	**2c**	48 h	 **5e**	51
6	**1d**	**2c**	48 h	no reaction	-

[a] **1** (1.5 mmol) was added to a solution of **2** (1.0 mmol) and $Cu(OTf)_2$ (0.1 mmol) in CH_3CN (1.5 ml) and stirred at room temperature. [b] Isolated yields after column chromatography.

Table 3. Addition of other weakly basic nitrogen nucleophiles to the acceptor **2c**

entry[a]	nucleophile	time	product	yield[%][b]	byproducts[b]
1	 **6a**	48 h	 **7a**	92	-
2	 **6b**	24 h	 **7b**	91	-
3	 **6c**	24 h	 **7c**	70	-
4	 **6d**	1 h	 **7d**	62	 **8d**[c] (23%)

[a]**6** (1.5 mmol) was added to a solution of **2c** (1.0 mmol) and $Cu(OTf)_2$ (0.1 mmol) in CH_3CN (1.5 ml) and stirred at room temperature. [b]Isolated yields after column chromatography. [c]Only one diastereomer was detected by NMR.

$\delta = 7.93$ (d, $J = 7.5$ Hz, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.44 (m_c, 2H), 7.40–7.20 (m, 5H), 5.45 (br s, 1H), 5.09 (s, 2H), 4.05 (m_c, 1H), 3.35 (dd, $J = 16.7$, 4.7 Hz, 1H), 3.06 (dd, $J = 16.7$, 5.9 Hz, 1H), 1.70–1.60 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 199.3$ (C_{quart}), 156.5 (C_{quart}), 137.3 (C_{quart}), 137.0 (C_{quart}), 133.7 (aryl-CH), 129.1 (aryl-CH), 128.9 (aryl-CH), 128.7 (aryl-CH), 128.5 (aryl-CH), 128.4 (aryl-CH), 66.9 (CH_2), 50.4 (CH), 42.7 (CH_2), 27.6 (CH_2), 11.2 (CH_3). IR (film) $\nu_{max}/cm^{-1} = 3321$, 2963, 1681, 1534, 1279, 1245, 1217, 1075, 1026, 970. HRMS (ESI+) m/z calcd for $C_{19}H_{21}NO_3Na$ (M^++Na) 334.1419, found 334.1432.

Acknowledgements

Support by the Fonds der Chemischen Industrie, St. John's College and the Studienstiftung des deutschen Volkes (T.C.W.) is gratefully acknowledged. Dr. Christian Stark is thanked for helpful discussions.

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