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A solvent-free method for the direct synthesis of Cbz-protected β-amino ketones using triphenylphosphine dibromide

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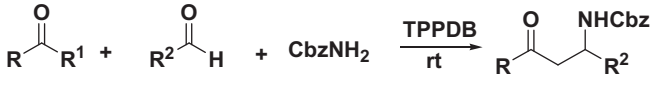
ABSTRACT

Triphenylphosphine dibromide (TPPDB) has been found to be a very effective catalyst for the one pot three-component Mannich reactions of aryl aldehyde, acetophenone, and benzyl carbamate under solvent-free condition at room temperature. The advantageous features of this methodology are operational simplicity, shorter reaction time, cost-effectiveness, and excellent yields. The catalyst possesses distinct advantages over other catalysts used for this conversion.

Chemical transformations are experiencing a deep change to meet sustainability criteria imposed by the Green Chemistry principles. In this context, the solventless approach is simple with amazing versatility. Organic reactions under solvent-free conditions are advantageous because of their enhanced selectivity and efficiency, ease of manipulation, and cleaner product formation, as toxic or volatile solvents are avoided.[1]

Multicomponent coupling reactions (MCRs) are emerging as useful tools for the carbon–carbon and carbon heteroatom bond-forming reactions and for the synthesis of small drug-like molecules with several degrees of structural diversity.[2] Additionally, MCRs are often environmentally benign and atom economic as well as they avoid time-consuming and costly purification processes and protection–deprotection steps. The Mannich reaction is one such multicomponent reaction and is the most widely utilized chemical transformation for construction of β-amino ketones and other β-amino carbonyl compounds, which in turn are important synthetic intermediates for various pharmaceuticals, natural products, and so forth.[3] Procedures exist in the literature for MCR synthesis of Cbz-protected β-amino ketones,[4] but most of them require solvents as reaction media, employ costly catalysts and reagents or toxic metal salts. They also suffer from drawbacks such as the use of a high catalyst loading and low yields.[5] Additionally, most of these methods use anilines or benzyl amine as nitrogen source and hence deprotection of the resulting amino-compound is difficult. Thus, the development of alternative efficient methods for the synthesis of β-amino ketones is highly desirable.

Triphenylphosphine dibromide (Ph_3PBr_2)[6] is a readily accessible, cheap, and highly effective reagent, as well as a catalyst for various organic transformations, such as bromination of alcohols, phenols, and enols, cleavage of ethers and acetals to alkyl



R= alkyl, aryl
R^1= Me
R^2= aryl, heteroaryl

Scheme 1.

Table 1
Catalytic systems for the synthesis of Cbz-protected β-amino ketones

Entry	Catalyst	Time (h)	Solvent	Yield (%)	Refs.
1	$AuCl_3$-PPh_3 (5 mol%)	24	CH_3CN	82	4a
2	I_2 (10 mol%)	24	CH_3CN	78	4a
3	PPh_3Br_2 (5 mol%)	12	—	80	This work

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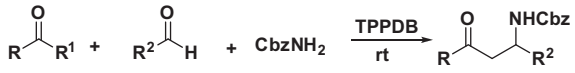
Table 2
TPPDB catalyzed Mannich reaction for the synthesis of Cbz-protected β-amino ketones



Entry	R-	R^1-	R^2-	Time (h)	Yield[a] (%)
1	Phenyl-	Me-	Phenyl-	12	80
2	4-Bromo-phenyl-	Me-	4-MeO-phenyl-	10	85
3	Phenyl-	Me-	2,4-Dichloro-phenyl-	13	79
4	Phenyl-	Me-	3,4-Dichloro-phenyl-	13	75
5	Phenyl-	Me-	4-Bromo-phenyl-	10	80
6	Phenyl-	Me-	2-Napthyl-	10	80
7	Phenyl-	Me-	4-Benzyloxy-phenyl-	13	75
8	4-Bromo-phenyl-	Me-	Phenyl-	12	70
9	4-Chloro-phenyl-	Me-	4-MeO-phenyl-	12	80
10	4-Bromo-phenyl-	Me-	4-Benzyloxy-phenyl-	12	80
11	4-Bromo-phenyl-	Me-	2-Napthyl-	13	75
12	4-Chloro-phenyl-	Me-	2-Napthyl-	14	75
13	Phenyl-	Me-	4-Nitro-phenyl-	12	79
14	-Cyclohepta-		4-MeO-phenyl-	10	80
15	-Cyclohexa-		4-MeO-phenyl-	10	80
16	-Cyclohexa-		Phenyl-	10	75
17	-Cyclohepta-		Phenyl-	12	75
18	4-Me-phenyl-	Me-	4-Methyl-phenyl-	10	85
19	4-Chloro-phenyl-	Me-	Phenyl-	12	80
20	Phenyl-	Me-	4-MeO-phenyl-	12	85
21	Phenyl-	Me-	2-Thiophen-	10	80

[a] Isolated yield and products were characterized by IR, NMR, and elemental analysis.

bromides, cyclization of β- and γ-amino alcohols to aziridines[7] and azetidines, conversion of carboxylic acid derivatives into acyl bromides, bromination or dehydration of carboxamides groups, or epoxide opening to vicinal dibromides, esterification of carboxylic acids,[8] preparation of nitrosamines and azides from the corresponding amines and hydrazines, deoxygenation of sulfoxides to the corresponding sulfides, synthesis of β-haloamines through the ring opening of aziridines etc. In the context of our study aimed at improving the ecocompatibility of certain organic processes, we report herein a mild, efficient, and simple procedure for the direct synthesis of Cbz-protected β-amino ketones using triphenylphosphine dibromide (TPPDB) as catalyst under solvent-free conditions at room temperature (Scheme 1).

We have observed that upon simple mixing of aldehyde (1 mmol), acetophenone (1 mmol), benzylcarbamate (1.2 mmol), and triphenylphosphine dibromide (5 mol%) quantitative conversion to β-keto carbamate was observed with excellent isolated yields. For comparison, the reaction was also carried out in organic solvents, such as CH_2Cl_2, THF, diethyl ether, CH_3CN, DMF, nitromethane, and methanol. Good yields of products were also formed in organic solvents such as CH_3CN and CH_2Cl_2 after 1–2 h of stirring at room temperature. In the absence of TPPBD, the reaction failed to provide the desired product even after stirring for longer duration. On the contrary, we observed that under solvent-free conditions at room temperature, the reaction proceeded to completion in one-pot, affording the β-keto carbamate in excellent yield.

The efficacy and generality of the catalyst TPPDB with some reported catalyst such as $AuCl_3$-PPh_3 and I_2 for the synthesis of Cbz-protected β-amino ketones can be gauged by comparison (Table 1). It is found that TPPDB was faster, cost-effective, and simpler than the existing methods.

A variety of structurally diverse aromatic aldehydes underwent the one-pot reaction smoothly without using any solvent to afford the corresponding β-keto carbamates in excellent yields.[9] The results are summarized in Table 2. Aromatic aldehydes bearing functional groups such as $-CH_3$, –OMe, –Cl, –Br, and $-NO_2$ as well as heteroatom containing aldehydes reacted efficiently to give the corresponding β-keto carbamates in high yields irrespective of the substituent position on the aromatic ring (Table 2).

In conclusion, we have demonstrated the efficacy and generality of triphenylphosphine dibromide as a versatile reagent for the synthesis of β-amino carbonyl compounds under solvent-free condition. It is worth mentioning that this metal-free method is faster, cost effective, and simpler than most of the existing methods and likely to attract attention of organic as well as medicinal chemists.

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9. Experimental section:
(a) *General experimental procedure:* Triphenylphosphine dibromide (5 mol%) was

added to a mixture of benzaldehyde (1 mmol), carbamate (1 mmol), and acetophenone (1 mmol), and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with EtOAc (2×10 mL), dried over anhydrous Na_2SO_4, and concentrated and purified by column chromatography on silica gel (60–120 mesh) with petroleum ether–EtOAc as eluent.

(b) *General experimental procedure for solid substances:* Triphenylphosphine dibromide (5 mol%) was added to a mixture of aldehyde (1 mmol), carbamate (1 mmol), and ketone (1 mmol) in a mortar. The reaction mixture was ground with a pestle to produce a homogeneous powder, and the mixture was left at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, to the solid was added 5 mL of water and the reaction mixture was extracted with EtOAc (2×10 mL), dried over Na_2SO_4, and concentrated and purified by column chromatography on silica gel (60–120 mesh) with petroleum ether–EtOAc as eluent.

3-(4-Bromo-phenyl)-1-(4-methoxy-phenyl)-3-oxo-propyl-carbamic acid benzyl ester (entry 2): White solid; Mp 142–143 °C; IR ($CHCl_3$) cm^{-1}: 2921, 2852, 1702, 1583, 1396, 1029, 695; ^1H NMR (300 MHz, $CDCl_3$): 7.9 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.23–7.33 (m,7H), 6.82 (d, J = 8.6 Hz, 2H), 5.68 (br s, 1H), 5.23 (m, 1H), 5.08 (s, 2H), 3.76 (s, 3H), 3.65 (d, J = 14.8 Hz, 1H), 3.34 (dd, J_1 = 6.6 Hz, J_2 = 6.6 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$): 196.9, 158.9, 155.6, 136.3, 135.3, 133.0, 131.9, 129.6, 128.6, 128.5, 128.1, 127.6, 114.0, 66.8, 55.2, 51.4, 44.1; Anal. Calcd for $C_{24}H_{22}NO_4$: C 74.21%, H 5.71%, N 3.61%. Found: C 74.20%, H 5.72%, N 3.59%.

1-(3,4-Dichloro-phenyl)- 3-oxo-propyl-carbamic acid benzyl ester (entry 4): White solid; Mp 140–163 °C; IR ($CHCl_3$) cm^{-1}: 3455, 2924, 2853, 1681, 1597, 1385, 1074, 689; ^1H NMR (300 MHz, $CDCl_3$): 7.89 (d, 2H), 7.43 (m, 11H), 6.0 (br s, 1H), 5.23 (m, 1H), 5.09 (s, 2H), 3.65 (d, J = 10 Hz, 1H), 3.40 (dd, J_1 = 6 Hz, J_2 = 6 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$): 197.4, 155.8, 141.9, 136.2, 136.1, 135.8, 133.7, 132.6, 131.3, 130.5, 128.8, 128.5, 128.3, 128.2, 128.1, 125.9, 60.4, 50.7, 43.5; Anal. Calcd for $C_{23}H_{19}NO_3$: C 64.50%, H 4.47%, N 3.27%. Found: C 64.51%, H4.48%, N 3.29%.

1-(4-Benzyloxy-phenyl)-3-oxo-3-phenyl-propyl-carbamic acid benzyl ester (entry 7): White solid; Mp 94–103 °C; IR ($CHCl_3$) cm^{-1}: 3335, 2918, 2850, 1686, 1596, 1290, 1039, 771; ^1H NMR (300 MHz, $CDCl_3$): 7.87 (d, J = 9 Hz, 2H), 7.42 (m, 15H), 6.91(d, J = 6 Hz, 2H), 5.79 (br s, 1H), 5.28 (m, 1H), 5.08 (s, 2H), 5.01 (s, 2H), 3.66 (d, J = 12 Hz, 1H), 3.38 (dd, J_1 = 6 Hz, J_2 = 9 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$): 198.0, 158.1, 155.7, 136.9, 136.6, 136.4, 133.4, 128.7, 128.6, 128.5, 128.1, 128.0, 127.6, 127.5, 114.9, 70.0, 66.8, 51.3, 43.6; Anal. Calcd for $C_{30}H_{27}NO_4$: C 77.40%, H 5.85%, N 3.01%. Found: C 77.41%, H 5.88%, N 3.0%.

3-(4-Chloro-phenyl)-1-naphthalen-2-yl-3-oxo-propyl-carbamic acid benzylester (entry 12): Pale yellow solid; Mp 151 °C; IR ($CHCl_3$) cm^{-1}: 3332, 3059, 1691, 1588, 1241, 1044.2, 696; ^1H NMR (300 MHz, $CDCl_3$): 7.81 (m, 6H), 7.40 (m, 10H), 5.89 (s, 1H), 5.46 (m, 1H), 5.1 (s, 2H), 3.74 (d, J = 15.4 Hz, 1H), 3.48 (dd, J_1 = 5.2 Hz, J_2 = 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 196.6, 155.8, 139.9, 136.3, 134.8, 133.2, 132.7, 129.5, 129.0, 128.6, 128.5, 128.1, 128.0, 127.6, 126.3, 126.0, 125.2, 124.4, 66.9, 51.9, 43.9; Anal. Calcd for $C_{27}H_{22}ClNO_3$: C 73. 05%, H 5.00%, N 3.16%. Found: C 73.04%, H 5.01%, N 3.15%.

3-Oxo-3-phenyl-1-thiophen-2-yl-propyl-carbamic acid benzyl ester (entry 21): Yellow oil; IR ($CHCl_3$) cm^{-1}: 3323, 3064, 1686, 1220, 1041; ^1H NMR (300 MHz, $CDCl_3$): 7.90 (d, J = 7.44 Hz, 2H), 7.24–7.84 (m, 8H), 7.15 (d, J = 4.8 Hz, 1H), 6.88 (m, 2H), 5.98 (d, J = 8.4 Hz, 1H), 5.55 (m, 1H), 5.11 (s, 2H), 3.73 (d, J = 13.8 Hz, 1H), 3.47 (dd, J_1 = 5.9 Hz, J_2 = 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 197.6, 155.6, 145.0, 136.5, 136.3, 133.5, 133.3, 128.7, 128.5, 128.1, 128.0, 126.8, 124.5, 66.9, 47.9, 43.5; Anal. Calcd for $C_{21}H_{19}NO_3S$: C 69.02%, H 5.24%, N 3.83%. Found: C 69.00%, H 5.27%, N 3.80%.