

A novel one-pot conversion of amines to homologated esters in poly(ethylene glycol)[☆]

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Abstract—The first deaminative homologation of amines ($-\text{CH}_2\text{NH}_2$) to esters ($-\text{CH}_2\text{CH}_2\text{COOEt}$) in one-pot is reported. The reaction proceeds through, formation of an aldehyde from an amine in the presence of Pd/C as catalyst followed by Wittig reaction and catalytic hydrogenation using poly(ethylene glycol) as the solvent in one-pot.

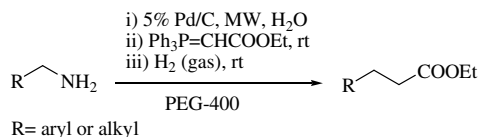
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The importance of one-pot reactions was recognized early in the history of organic synthesis.¹ Useful chemical products can be produced in one-pot with less waste and greater economic benefits by avoiding lengthy separation and purification of the intermediate compounds.² Creating one-pot synthetic routes is a challenge and the most important factors are the choice of solvent and selection of a reagent/reaction which enables the desired conversion efficiently. Poly(ethylene glycol) (PEG) has recently received considerable attention as an inexpensive, non-toxic, thermally stable reusable solvent by us³ and others.⁴ Also, Pd/C is a stable catalyst which tolerates a reasonable environment. Taking advantage of this combination and also to add a new dimension in one-pot reactions, we designed a transformation wherein the initially added catalyst (in this instance Pd/C required for conversion of the amine to an imine) will also act as a catalyst for the hydrogenation of the olefin generated upon Wittig reaction. This procedure would allow one to convert an amine to a two-carbon homologated ester in one-pot involving three chemical transformations.

The conversion of an amine to a carbonyl compound has been reported with various metal oxidizing reagents such as KMnO_4 ,⁵ K_2FeO_4 ,⁶ $\text{Pb}(\text{OAc})_4$,⁷ NiO_2 ⁸ and $\text{HgO}-\text{I}_2$ ⁹ and as a biological process.¹⁰ A two-step pro-

cess is also available, where an amine was converted to an imine using a strong base such as *n*-BuLi or DBU with subsequent hydrolysis to obtain ketones.¹¹ However, these methods suffer from disadvantages such as the requirement of larger amounts of reagents, anhydrous reaction conditions and low yields of the products. Recently, Miyazawa et al. reported the conversion of an amine to a ketone using water as the solvent (oxygen source) albeit with limited substrates.¹² However, this reaction strongly depends on the structure of the reactant, especially the number of hydrogens on the carbon adjacent to the nitrogen and also affords unwanted by-products. Herein we report a novel transformation of amines to homologated esters in one-pot using poly(ethylene glycol) as the solvent (Scheme 1).

Initially, benzylamine, 5% Pd/C and poly(ethylene glycol)-400 were taken in a pressure resistant glass ampoule and the mixture was subjected to microwave irradiation at 170 °C for 3 h. After cooling to room temperature, a 68% yield of benzaldehyde was obtained after workup by ether extraction (Table 1, entry 1). The same reaction was carried out by conventional heating at 170 °C and a similar result was obtained after 9 h (Table 1, entry 2). Based on the above observations, we conducted further



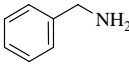
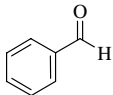
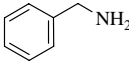
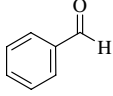
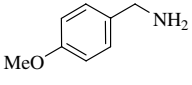
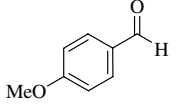
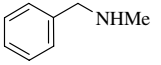
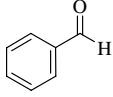
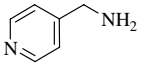
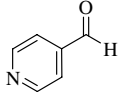
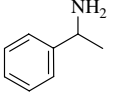
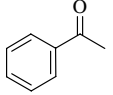
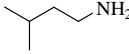
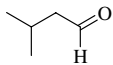
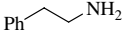
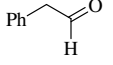
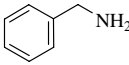
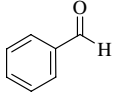
Scheme 1.

Keywords: Palladium; One-pot reaction; Poly(ethylene glycol); Amines; Esters.

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Table 1. Conversion of amines to carbonyl compounds^a

Entry	Amine	Carbonyl compound	Yield ^b (%)
1			68
2 ^c			70
3			70
4			74
5			66
6			69
7			18
8			26
9 ^d			66

^a Reaction conditions: 5% Pd/C, PEG-400, MW, 3 h.

^b Determined by GC and GC-MS.

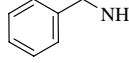
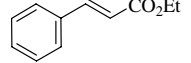
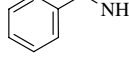
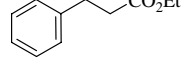
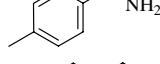
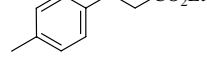
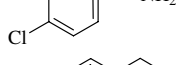
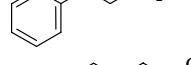
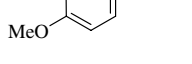
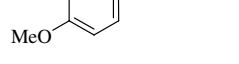
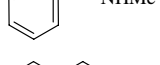

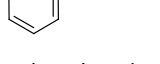

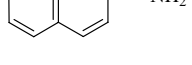
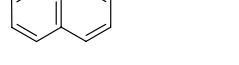
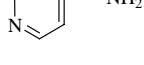
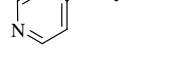


^c Conventional heating at 170 °C for 9 h.

^d The reaction was performed over three runs in the same pot without substantial loss of activity.

reactions using various benzylamines including *N*-methyl benzylamine and 2-aminophenyl ethane (Table 1, entries 3–6) in the presence of 5% Pd/C in poly(ethylene glycol) under microwave irradiation. Satisfactory results were obtained and are summarized in Table 1. However, aliphatic amines (Table 1, entries 7 and 8) gave low yields of the desired products. Recycling of the reagent system (Pd/C in PEG) was also successfully achieved (Table 1, entry 9).

With these positive results in hand, we next investigated the Wittig reaction of the aldehyde in the same vessel. Accordingly, benzylamine was subjected to the above mentioned reaction conditions under microwave irradiation for 3 h and then cooled to room temperature, after which water was added. After stirring for 30 min, the two-carbon stable ylide (ethoxycarbomethylene)tri-phenylphosphorane was added to the same reaction vessel and the mixture stirred at room temperature for 12 h to afford the expected α,β -unsaturated ester in a 65%

Table 2. One-pot conversion of an amine to a homologated ester^a

Entry	Amine	Ester ^b	Yield ^c (%)
1			65
2			60
3			61
4			62 ^d
5			60
6			64
7			57
8			50
9			54
10			21

^a For reaction conditions see Ref. 13.

^b All the products were characterized by ¹H NMR and mass spectroscopy.

^c Isolated yields.

^d Dechlorination occurred.

yield (Table 2, entry 1). After successful one-pot conversion of an amine to an unsaturated homologated ester, we next attempted the reduction of the double bond using hydrogen gas in the same vessel and obtained the desired saturated ester in 60% yield (Table 2, entry 2).¹³ The initially added 5% Pd/C was still active enough for further reduction of the olefin. Encouraged by this interesting result, our attention was transferred to the other amines and the results are summarized in Table 2.¹⁴

When a variety of substituted benzylamines bearing different groups were employed, the reactions proceeded smoothly to give the desired homologated esters in reasonably good yields (Table 2, entries 3–5). *N*-Substituted benzylamines and 2-naphthyl methylamine also proved to be good substrates in the reaction, giving the corresponding esters in good yields (Table 2, entries 6–8). The Wittig products of entries 9 and 10 (Table 2) on hydrogenation gave a complex mixture of products. However, the pure α,β -unsaturated esters could be obtained on work-up.

In summary, we have successfully demonstrated the one-pot conversion of amines to homologated esters using

poly(ethylene glycol) as the solvent. Further investigations aimed at improving the yields and applications are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.12.035](https://doi.org/10.1016/j.tetlet.2006.12.035).

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- Representative experimental procedure*: A mixture of benzylamine (0.25 g, 2.33 mmol), 5% Pd/C (125 mg) and poly(ethylene glycol)-400 (5 ml) in a pressure resistant glass ampoule was subjected to microwave irradiation (100 W, CEM Discover, 2.45 GHz, CEM Corporation, NC, USA) at 170 °C. After 3 h, the reaction mixture was cooled to room temperature; water was added and the reaction stirred at room temperature for 30 min. To the same reaction vessel, (ethoxycarbomethylene)triphenylphosphorane (1.2 g, 3.5 mmol) was added and stirring was continued at room temperature. After 12 h, the reaction mixture was subjected to hydrogenation (hydrogen gas balloon) at room temperature. After completion of the reaction (8 h), the mixture was extracted with diethyl ether, the combined organics dried (Na₂SO₄) and evaporated in vacuo to give a crude residue which was purified by column chromatography (Table 2, entry 2).
- Spectroscopic data for selected products: (Table 2, entry 1): ¹H NMR (CDCl₃, 300 MHz): δ 7.69 (d, *J* = 15.8 Hz, 1H), 7.53–7.52 (m, 2H), 7.39–7.38 (m, 3H), 6.44 (d, *J* = 5.8 Hz, 1H), 4.27 (q, *J* = 6.8 Hz, 2H), 1.34 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 166.2, 143.9, 133.9, 129.5, 128.2, 127.4, 117.7, 59.8, 13.6; EIMS (*m/z*): 199.1 (M+Na)⁺. (Table 2, entry 2): ¹H NMR (CDCl₃, 300 MHz): δ 7.30–7.09 (m, 5H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 172.3, 140.0, 127.9, 127.7, 125.7, 59.8, 35.4, 30.4, 13.6; EIMS (*m/z*): 201.1 (M+Na)⁺. (Table 2, entry 10): ¹H NMR (CDCl₃, 200 MHz): δ 7.42–7.00 (m, 6H), 5.81 (d, *J* = 15.6 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.52 (d, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 50 MHz): δ 166.4, 147.2, 137.6, 128.7, 128.6, 126.6, 122.3, 60.2, 38.4, 14.2; EIMS (*m/z*): 213.2 (M+Na)⁺. See Supplementary data for ¹H NMR and ¹³C NMR spectra of the products.