A Mild and Efficient Method for the One-Pot Monocarboxymethylation of Primary Amines

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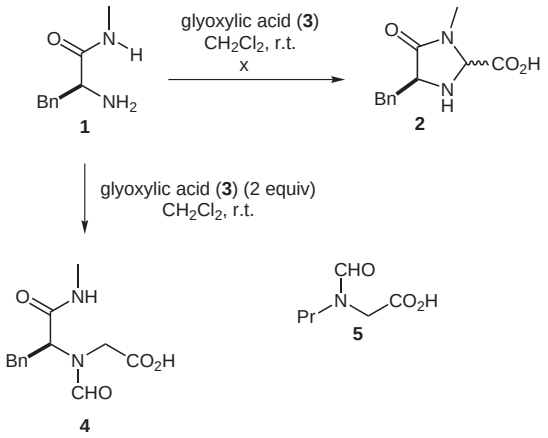
Abstract: A mild and efficient method for the monocarboxymethylation of primary amines that takes place under aqueous conditions at room temperature is described. Treatment of an aqueous solution of a variety of primary amines with two equivalents of glyoxylic acid leads to the *N*-formyl glycine derivatives. Direct hydrolysis of the crude reaction solution leads to the products of amine monocarboxymethylation in good to excellent yield.

Key words: metal-free synthesis, amino acids, glycine derivatives

The development of robust synthetic methods of broad utility is of primary concern. Within this context, addition to existing methodology that results in cheaper, more efficient and convenient processes provides the driving force behind much research.

Small organic molecules containing amides and peptidomimetics represent a fundamental class of bioactive compound of which N-alkylated glycine derivatives are an important subsection.[1] The most widely method used for the introduction of *N*-alkyl glycines is the alkylation of primary amines with α-halo acids and esters.[2] Although well developed, the reaction frequently suffers from problems of overalkylation which can be circumvented by the addition of excess amine or the acceptance of poor yields.

Within an ongoing project concerned with the discovery of efficient molecular scaffolds for amino catalytic transformations[3] we reacted the amino amide **1** with one equivalent of glyoxylic acid (**3**) in dichloromethane at room temperature with the aim of preparing the imidazolidinone **2** (Scheme 1).[4] This reaction failed to deliver the expected product, the *N*-formyl glycine derivative **4** being isolated in 38% yield (together with unreacted starting material **1**). Conducting the reaction in the presence of two equivalents of glyoxylic acid gave **4** in 74% yield. An exhaustive search of the literature revealed an isolated report of this class of transformation for the reaction of primary amines with glyoxylic acid using either trifluoroacetic acid or formic acid as the reaction solvent.[5] For example, reaction of propylamine with 2.05 equivalents of glyoxylic acid at 70 °C for 14 hours gave the *N*-formyl derivative **5** in 93% isolated yield. Although efficient, we believed our conditions were significantly milder than those previously reported and warranted further examination. Within this letter we report a mild and efficient route for the conversion of primary amines to their *N*-formyl glycine and glycine analogues, expand the scope of the transformation and describe the application of this procedure to the reaction of diamines.



Scheme 1 Attempted synthesis of imidazolidinone **2**

Initial optimisation studies were conducted on the reaction between phenethylamine (**6**) and glyoxylic acid (**3**, Table 1). The reaction was reasonably efficient in a broad spectrum of reaction solvents over the 24 hour period (entries 1–7), with the optimal solvent being water (entry 8). Stirring one equivalent of phenethylamine (**6**) with two equivalents of glyoxylic acid monohydrate (**3**) at room temperature for 24 hours cleanly gave the *N*-formyl adduct **7** in 75% isolated yield. Although water is frequently cited as a 'green' solvent (even when large quantities of organic solvents are often used in compound isolation and purification), we believe the specific advantage of using an aqueous environment for this transformation is that it allows for the direct one-pot conversion to the synthetically useful *N*-alkyl glycine derivative **8** without isolation of the formylated intermediate **7**. Thus, addition of 2 M HCl directly to the crude reaction mixture and heating the resulting solution for five hours led to **8** which could easily be isolated by crystallisation (entry 9). The reaction sequence was equally effective using 1 M aqueous glyoxylic acid solution to prepare both the intermediate **7** (entry 10, 77%) and the glycine derivative **8** (entry 11, 69%).

Having developed mild and efficient conditions for the one-pot carboxymethylation of phenethylamine we went on to examine some of the scope of the transformation.[6]

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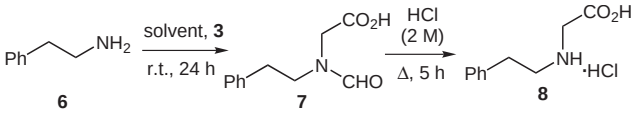
Table 1 Examination of Solvent Systems[a]



6 7 8

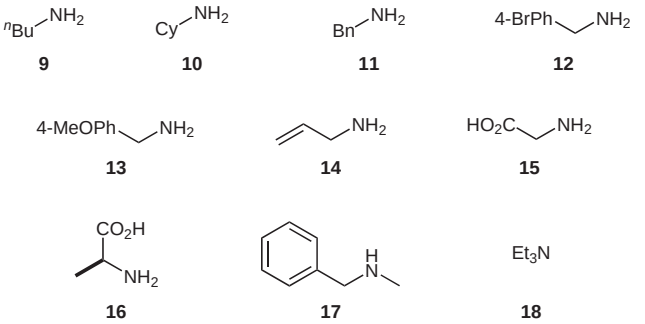
Entry	Solvent	Conversion (%)
1	CH_2Cl_2	72[e]
2	Et_2O	49[d]
3	EtOAc	64[d]
4	MeOH	23[d]
5	MeCN	45[d]
6	PhMe	43[d]
7	THF	30[d]
8	H_2O	75[d]
9[c]	H_2O	70[e]
10[b]	H_2O	77[d]
11[b,c]	H_2O	69[e]

[a] All reactions performed at r.t. for 24 h at 0.2 M concentration using glyoxylic acid monohydrate unless otherwise stated.
[b] Reaction conducted using commercial 1 M glyoxylic acid solution.
[c] Isolated yield of 2-(phenylethylamino)acetic acid (**8**).
[d] Determined from ^{1}H NMR of crude reaction mixture.
[e] Isolated yield.

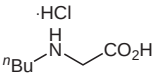
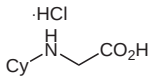
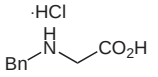
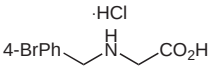
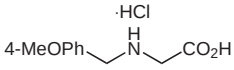
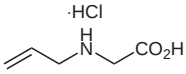
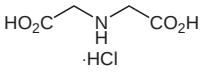
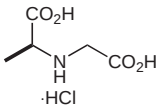
The reaction was equally efficient with primary and secondary α-substitution of the reactive nitrogen (entry 1, 78%; entry 2, 86%) suggesting a broad range of substituted amines will participate in the process. Benzylic substrates were also efficient (entry 3, 79%) with electron-donating and -withdrawing substitution on the aromatic ring also being tolerated (entry 4, 60%; entry 5, 68%). Functional groups such as alkenes (entry 6, 25%) and carboxylic acids (entry 7, 54%; entry 8, 77%) are also permitted.

The precise mechanism by which the reaction proceeds is unclear at present; a possible mechanism explaining the observed outcome is outlined in Scheme 2. From the stoichiometry of the reaction (2 equiv glyoxylic acid) it is not possible for the glyoxylic acid to act as a hydride source in an analogous manner to formic acid in the reductive amination of aldehydes.[7] This suggests the imine **28**, resulting from the condensation of the amine **27** with glyoxylic acid (**3**), adds to a second molecule of glyoxylic acid to give the intermediate **29**. The ensuing decarboxylation would then lead to the observed product **31** after protonation. Imines derived from the reaction of primary amines and glyoxylic acid are well known and characterised[8] and have been exploited as reactive intermediates in tandem reaction processes including the Diels–Alder reaction[9] and nucleophilic additions of nitro alkanes.[10] The action of imines as nucleophiles is less frequently utilised as a synthetic technique, although is well established in, for example, *N*-acyliminium chemistry.[11]

Table 2 Scope of the Transformation[a]

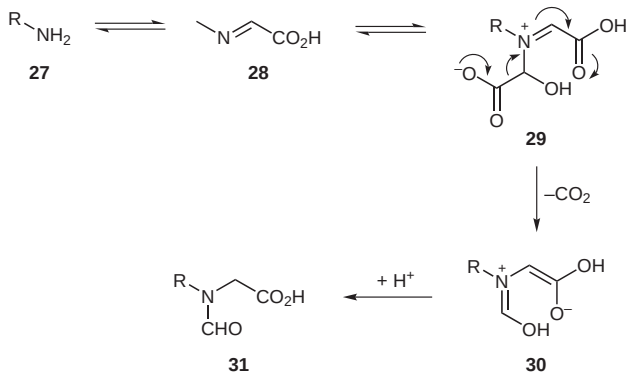


9 10 11 12 13 14 15 16 17 18

Entry	Amine	Product	Yield (%)
1	**9**	 **19**	78
2	**10**	 **20**	86
3	**11**	 **21**	79
4	**12**	 **22**	60
5	**13**	 **23**	68
6	**14**	 **24**	25
7	**15**	 **25**	54
8	**16**	 **26**	77
9	**17**	no reaction	–
10	**18**	no reaction	–

[a] All reactions performed at r.t. for 24 h at 0.2 M concentration using glyoxylic acid monohydrate followed by addition of 2 M HCl and heating for 5–18 h.

Within the examination of the scope of the reaction we confirmed that both secondary (Table 2, entry 9) and tertiary amines (Table 2, entry 10) were returned unreacted

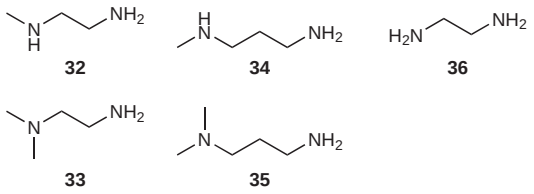


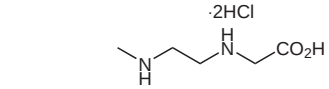
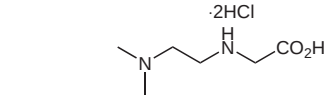
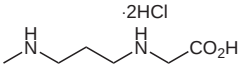
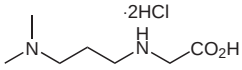
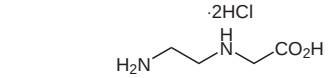
Scheme 2 Possible mechanism for the observed transformation

after exposure to the standard reaction conditions. This opened the possibility to react a series of diamine substrates that would further exemplify the strength of the methodology. In the alkylation of diamines using alkyl halides, selective functionalisation of a primary amine in the presence of either a secondary or tertiary amine is difficult and frequently relies on protecting-group strategies.[12] The current work allows for chemospecific reaction of a primary amine in the presence of both secondary and tertiary amines (Table 3). For example, reaction of *N*-methylethylenediamine (**32**) with glyoxylic acid monohydrate (**3**) at room temperature followed by addition of 2 M hydrochloric acid and refluxing the resulting solution for 18 hours led to the glycine derivative **37** in 41% isolated yield. The protocol was equally effective for the diamines **33**–**35** giving the corresponding monocarboxymethylated products **38**–**40** in 44–68% yield (Table 3, entries 2–4). The monocarboxymethylated derivative of ethylenediamine **41** has been used by Bradley in the preparation of PNA–peptide conjugates.[13] This was prepared by the addition of a large excess of ethylenediamine (10 equiv) to α-bromoacetic acid.[14] A more convenient access to this compound can be achieved using one equivalent of ethylenediamine **36** and glyoxylic acid monohydrate (**3**) which gave the monocarboxymethylated adduct in 31% isolated yield after crystallisation of the product from methanol (Table 3, entry 5).

In summary, we have developed a simple one-pot procedure for the monocarboxymethylation of primary amines. The reaction is operationally simple and applicable to a broad range of substrates. Significantly, the reaction does not work on secondary amines and thus allows for the chemospecific reaction of unprotected diamines, which is not the case for alternative methods for this class of bond construction. All the products reported were easily crystallised from methanol–diethyl ether, greatly simplifying the experimental protocol. We are currently investigating the application of this methodology to the construction of piperazinones and will report on our findings shortly.

Table 3 Reaction of Diamines[a]



Entry	Amine	Product	Yield (%)
1	**32**	 **37**	41
2	**33**	 **38**	68
3	**34**	 **39**	44
4	**35**	 **40**	59
5	**36**	 **41**	31

[a] All reactions performed at r.t. for 24 h at 0.2 M concentration using glyoxylic acid monohydrate followed by addition of 2 M HCl and heating for 5–18 h.

Typical Experimental Procedure for the Monocarboxymethylation of Primary Amines

Glyoxylic acid monohydrate (**3**, 1.52 g, 16.5 mmol) was dissolved in distilled H_2O (40 mL) at r.t. Phenethylamine (**6**, 1.00 g, 8.25 mmol) was added and the resulting solution stirred for 24 h. During this time the formation of a white precipitate was observed. After this period 2 M HCl (20 mL, 40 mmol) was added and the reaction mixture heated at reflux overnight. The solvent was removed under reduced pressure and the residue recrystallised from MeOH–Et_2O to give 2-(phenylethylamino)acetic acid hydrochloride (**8**, 1.24 g, 70%) as a colourless solid; mp 184 °C. IR (Nujol): 2924, 1748 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 13.80 (br s, 1 H), 9.38 (br s, 2 H) 7.36–7.24 (m, 5 H), 3.89 (s, 2 H), 3.16 (t, *J* = 10.0 Hz, 2 H), 2.99 (t, *J* = 10.0 Hz, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.5 (s), 137.6 (s), 129.1 (d), 129.1 (d), 127.3 (d), 48.1 (t), 47.3 (t), 31.8 (t). MS (ES): *m/z* = 180 $[M + H - HCl]^+$. HRMS (ES): *m/z* calcd for $C_{10}H_{14}N_1O_2$ $[M + H - HCl]^+$: 180.1025; found: 180.1019.

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