Observations on the Reaction of *N*-Alkyloxazolidines, Isocyanides and Carboxylic Acids: A Novel Three-Component Reaction Leading to *N*-Acyloxyethylamino Acid Amides

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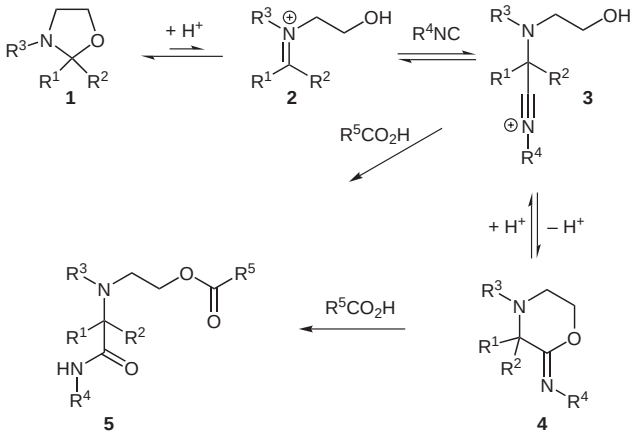
Abstract: *N*-Alkyloxazolidines, readily prepared by condensation of the parent carbonyl compounds with β-aminoalcohols, were found to undergo three-component reactions with isocyanides and carboxylic acids to give *N*-acyloxyethylamino acid derivatives in good yield. The reaction allows the variation of substituents at five different sites in the products through suitable choice of reagents.

Key words: amino alcohols, carboxylic acids, heterocycles, multicomponent reactions, ring opening

Isocyanide based multicomponent reactions have provided a wealth of highly useful sequences for the assembly of compound libraries of particular interest to the pharmaceutical industry, and those which incorporate amino acid or hydroxy acid motifs through the use of the well known Ugi[1] and Passerini[2] reactions have proven to be especially valuable. Numerous reviews[3] in recent years on the development and application of isocyanide based multicomponent reactions provide ample evidence of the burgeoning interest in this rapidly evolving research area.

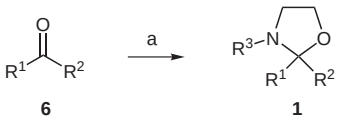
Within this framework, we were particularly interested in the chemistry of oxazolidines **1**, which readily undergo ring opening to iminium ions **2** and subsequent nucleophilic addition in the presence of organometallic reagents[4] and reducing agents.[5] In addition, Wilkins et al. have demonstrated that Lewis acid activation of the oxazolidine group will enable nucleophilic attack of furan and other electron-rich aromatic compounds,[6] and in a similar vein, Griengl and Bleikolm have shown that enol ethers can add into the oxazolidine ring to yield seven-membered ring acetal derivatives.[7]

Given that iminium cations play a central role in the Ugi reaction, we therefore reasoned, as shown in Scheme 1, that activation of the oxazolidine ring with protic acid or a Lewis acid would enable nucleophilic attack of an isocyanide to give nitrilium cation **3**. Subsequent direct capture of the carboxylic acid, followed by rearrangement via transfer of the acyl group from the acyclic *O*-acyl imidate to the pendant oxygen, in an analogous way to the Ugi or Passerini reactions,[1,2] would then provide an ethanolamine derived skeleton **5**. Alternatively, ring closure of the alcohol to form a morpholine ring **4**, followed by acid-catalysed ring opening with the carboxylic acid would also lead to **5**. The ethanolamine skeleton **5** therefore provides the opportunity for the introduction of diverse functionality in at least five different locations. During the course of our own preliminary study, a conceptually similar approach using tethered bis(secondary amine) derivatives in an Ugi-type four component reaction was recently disclosed by Giovenzana et al.[8]



Scheme 1

A range of oxazolidines[9] was synthesised from the parent carbonyl compounds by condensation with *N*-alkylethanolamines, either by repeated concentration of an ethanolic solution of the two components[10] or by heating in benzene or toluene under Dean–Stark water removal conditions[9,11] (Scheme 2 and Table 1).



Scheme 2 *Reagents and conditions*: a) $R^3NHCH_2CH_2OH$, EtOH (Method A) or $R^3NHCH_2CH_2OH$, I_2, toluene or benzene, Dean–Stark (Method B).

With the oxazolidines in hand, conditions were then investigated for the reaction of the *p*-tolualdehyde derivative **1a** with *tert*-butyl isocyanide and benzoic acid (Scheme 3 and Table 2). Without addition of an acid catalyst, the reaction was extremely slow, providing only a

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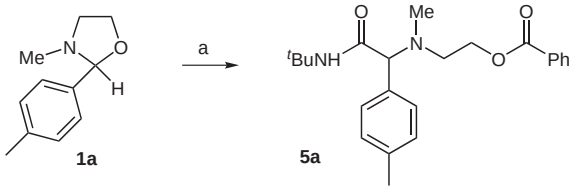
Table 1 Synthesis of Oxazolidines

R^1	R^2	R^3	Method	Yield	Product
p-Me-C_6H_4	H	Me	A	90%	**1a**
n-C_6H_{13}	H	Me	B	73%[a]	**1b**
p-MeO-C_6H_4	H	Me	A	77%[a]	**1c**
p-NO_2-C_6H_4	H	Me	A	60%[a]	**1d**
p-Me-C_6H_4	H	$PhCH_2$	A	97%	**1e**
$(CH_2)_5$		Me	A	86%[a]	**1f**
p-Me-C_6H_4	H	*t*-Bu	B	64%[a]	**1g**

[a] The product was purified by distillation.

14% yield of **5a** after heating under reflux for 24 hours. Since prolonged reaction times led to little improvement in this yield, acidic catalysts were investigated. Screening a wide range of solvents using Dowex acidic resin as a catalyst indicated that acetonitrile was optimal (only solvents which gave appreciable yields of the desired product are shown). Concurrently, *p*-TsOH was found to give a superior yield of the multicomponent product in THF. Finally, these observations directed us to use a catalytic amount of *p*-TsOH in acetonitrile, which pleasingly provided the multicomponent product **5a** in 66% yield.[12]

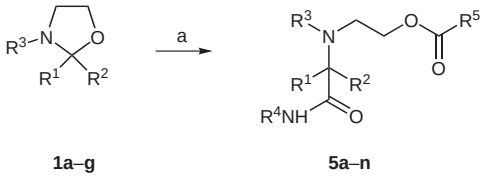


Scheme 3 *Reagents and conditions*: a) See Table 2.

Table 2 Optimisation of the Multicomponent Reaction

Catalyst	Solvent	Conditions	Yield
None	THF	reflux, 24 h	14%
Dowex	THF	reflux, 17 h	24%
Dowex	MeCN	reflux, 17 h	52%
Dowex	MeOH	reflux, 17 h	30%
Dowex	DMF	100 °C, 17 h	19%
Dowex	EtOAc	reflux, 17 h	38%
TsOH	THF	reflux, 24 h	56%
TsOH	MeCN	reflux, 24 h	66%

A variety of oxazolidines, isocyanides and carboxylic acids were then reacted under these conditions to yield the ethanolamine derivatives **5a**–**n** in good to excellent yields in most cases. Aliphatic and aromatic isocyanides were well tolerated, and both aldehyde and ketone derived oxazolidines readily reacted under the chosen conditions. A range of carboxylic acids could also be employed, including aliphatic, aromatic, and heterocyclic derivatives such as 3-(3-indole)propionic acid (**5g**). Larger substituents at R^3, however, may lead to lower yields of the multicomponent product (**5l** and **5n**, Scheme 4 and Table 3).

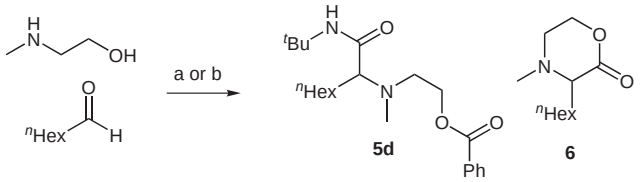


Scheme 4 *Reagents and conditions*: a) R^4NC, R^5CO_2H, TsOH (0.1 equiv), MeCN, 24 h, reflux.

Table 3 Multicomponent Reactions

Oxazolidine	R^4	R^5	Yield	Product
1a	*t*-Bu	Ph	66%	**5a**
1a	*t*-Bu	Et	64%	**5b**
1a	*c*-C_6H_{11}	Ph	71%	**5c**
1b	*t*-Bu	Ph	80%	**5d**
1b	*t*-Bu	Et	78%	**5e**
1b	*c*-C_6H_{11}	Ph	48%	**5f**
1b	*t*-Bu	2-(3-indole)ethyl	44%	**5g**
1b	2,6-dimethylphenyl	Et	42%	**5h**
1b	4-$MeOC_6H_4$	Ph	45%	**5i**
1c	*t*-Bu	Ph	68%	**5j**
1d	*t*-Bu	Ph	47%	**5k**
1e	*t*-Bu	Ph	44%	**5l**
1f	*t*-Bu	Ph	63%	**5m**
1g	*t*-Bu	Me	20%	**5n**

An attempt to combine the oxazolidine synthesis with the multicomponent reaction in a four-component reaction of *N*-methylethanolamine, heptanal, *tert*-butyl isocyanide and benzoic acid gave a 13% yield of the desired multicomponent product, together with a 25% yield of the lactone **6** (Scheme 5). The formation of lactone **6** provides strong evidence that the intermediate **3** must readily cyclise to morpholine **4** and that the two products **5d** and **6** are the result of a subsequent nucleophilic attack by benzoic acid and water, respectively. A subsequent reaction carried out in the absence of the carboxylic acid component gave the lactone **6** in 36% yield. The formation of **6** offers a complementary multicomponent approach to morpholin-2-one derivatives, to that reported by Kim et al., involving an Ugi-type reaction of glycolaldehyde dimer.[13]



Scheme 5 *Reagents and conditions*: a) *p*-TsOH (0.1 equiv), $PhCO_2H$ (1 equiv), *t*-BuNC (1 equiv), MeCN, reflux, 13% (**5d**), 25% (**6**); b) *p*-TsOH (1 equiv), *t*-BuNC (1 equiv), MeCN, reflux 36% (**6**).

In summary, a novel multicomponent reaction between an oxazolidine, an isocyanide, and a carboxylic acid has been developed which provides ethanolamine derivatives in good yield and readily allows the variation of functional groups at five different sites within the product. The *N*-acyloxyethylamino acid derivatives **5** provide a complementary product structure to those which are produced by the well established Ugi and Passerini reactions and we therefore anticipate that the reaction will be of value for compound library synthesis. Further work is underway on the extension of this and other related multicomponent reactions.

Acknowledgment

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References and Notes

(1) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8.

(2) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181.

(3) (a) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (c) Zhu, J. P. *Eur. J. Org. Chem.* **2003**, 1133. (d) Hulme, C.; Nixey, T. *Curr. Opin. Drug Discov. Devel.* **2003**, *6*, 921. (e) Domling, A. *Chem. Rev.* **2006**, *106*, 17.

(4) (a) Normant, J. F.; Germon, C.; Alexakis, A. *Bull. Soc. Chim. Fr.* **1984**, 377. (b) Senkus, M. *J. Am. Chem. Soc.* **1945**, *67*, 1515. (c) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F. *J. Med. Chem.* **1984**, *27*, 1067.

(5) (a) Bergmann, E. D.; Lavie, D.; Pinchas, S. *J. Am. Chem. Soc.* **1951**, *73*, 5664. (b) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Synlett* **2002**, 375.

(6) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 14381.

(7) (a) Bleikolm, A.; Griengl, H. *Tetrahedron Lett.* **1975**, 2565. (b) Bleikolm, A.; Griengl, H. *Liebigs Ann. Chem.* **1976**, 1783. (c) Bleikolm, A.; Griengl, H. *Liebigs Ann. Chem.* **1976**, 1791.

(8) Giovenzana, G. B.; Tron, G. C.; Di Paola, S.; Menegotto, I. G.; Pirali, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 1099.

(9) Bergmann, E. D. *Chem. Rev.* **1953**, *53*, 309.

(10) **Oxazolidine Preparation (Method A); General Procedure.** A solution of the amino alcohol (20 mmol) and aldehyde (20 mmol) in EtOH (20 mL) was stirred at r.t. for 90 min. The solvent was removed under reduced pressure; EtOH (3 × 10 mL) was added, then removed under reduced pressure repeatedly. The product was then dried under high vacuum to give the oxazolidine as a colourless oil.

(11) **Oxazolidine Preparation (Method B); General Procedure.** A trace of iodine was added to a solution of amino alcohol (174 mmol) and aldehyde (174 mmol) in anhyd benzene (125 mL). The reaction mixture was heated under Dean–Stark water-removal conditions for 90 min. After removal of the solvent under reduced pressure the residue was distilled under reduced pressure to give the oxazolidine as a colourless oil.

(12) **Multicomponent Reaction; Typical Procedure.** 2-Hexyl-3-methyloxazolidine (**1b**, 343 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*-TsOH (38 mg, 0.2 mmol) and *tert*-butyl isocyanide (166 mg, 2 mmol) were added to MeCN (5 mL) and refluxed under an atmosphere of nitrogen for 21 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (PE–EtOAc, 4:1) to yield 2-[(*tert*-butylcarbamoylheptyl)methylamino]ethyl benzoate (**5d**, 599 mg, 80%) as a colourless oil. R_f 0.34 (hexanes–EtOAc, 2:1). IR: 3365 br (NH), 3026, 2948, 2926, 2856 (CH), 1724, 1674 (C=O), 1506 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.74 (3 H, t, *J* = 6.9 Hz, Me), 1.16 (9 H, s, *t*-Bu), 1.17–1.41 (6 H, m, 3 × CH_2), 1.44–1.59 (2 H, m, CH_2), 1.62–1.77 (2 H, m, CH_2), 2.23 (3 H, s, NMe), 2.77–2.87 (3 H, m, CH_2N, CHN), 4.32–4.47 (2 H, m, CH_2O), 6.62 (1 H, br s, NH), 7.40 (2 H, t, *J* = 7.8 Hz, *m*-ArH), 7.53 (1 H, t, *J* = 7.8 Hz, *p*-ArH), 8.00 (2 H, d, *J* = 7.8 Hz, *o*-ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 27.2, 27.4, 28.6, 29.5, 31.6, 38.3, 50.2, 53.7, 62.7, 68.9, 128.3, 129.5, 130.0, 133.0, 166.4, 172.2. MS (FAB): *m*/*z* (%) = 378 (18), 377 (74, M + H^+), 375 (5), 277 (18), 276 (100), 154 (8). HRMS (FAB): *m*/*z* calcd for $C_{22}H_{37}N_2O_3$ [M + H]$^+$: 377.28042; found: 377.28061.

(13) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett.* **2001**, *3*, 4149.