A Versatile Synthesis of α-Amino Acid Derivatives via the Ugi Four-Component Condensation with a Novel Convertible Isonitrile

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Received 10 October 2003

Abstract: The Ugi four-component condensation (4CC) reaction with the carbonate-type isonitrile **9** proceeded smoothly, and subsequent base treatment of the Ugi products **10** provided the *N*-acyloxazolidinones **11** in high yield. The *N*-acyloxazolidinones derivatives can be reacted with several hetero-nucleophiles, namely, reaction of **11** with thiolates gave thiol ester derivatives **16** efficiently.

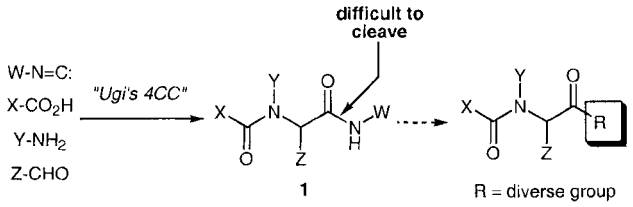
Key words: Ugi four-component condensation (4CC), α-amino acid derivatives, convertible isonitrile, *N*-acyloxazolidinones, thiol esters

Multi-component reactions (MCRs) have attracted much attention because of their use in the construction of combinatorial libraries.[1] In particular, the Ugi four-component condensation (Ugi's 4CC)[2] has been widely employed since it provides various α-amino amide derivatives **1** by a simple experimental procedure under mild conditions.[1b] These products possess a drug-like structure and could be responsible for a variety of important biological activities. Moreover, the great facility of the condensation to form amide bonds also permits the efficient total synthesis of complex natural products.[3]

Although numerous reports of the Ugi 4CC reaction have been published, inherent problems in the stereoselective construction of the α-position[4] and cleavage of the *C*-terminal amide still need to be solved. Due to the limited variety of isonitriles available in comparison with the other components, incorporation of other diverse functional groups at the *C*-terminal amide (R-groups) has been required for the generation of these libraries (Scheme 1).[5–11]

Recently, the 4CC reaction with the convertible isonitriles **2** and **3** was reported by Armstrong and Ugi, respectively (Figure 1). In the case of Armstrong's 1-cyclohexenyl isocyanide (**2**),[5] the nucleophilic addition to the amide bond of the Ugi products was readily carried out under acidic conditions. On the other hand, the condensation product derived from the isocyanoalkyl alkyl carbonates **3** reported by Ugi was converted to the corresponding α-amino ester derivatives **6** by treatment with base.[6] As shown in Scheme 2, this reaction would take place via the formation of the *N*-acyloxazolidinones **5** by cyclization of the amide anion onto the carbonate of **4** followed by addition of the alkoxide ($^-$OR) and elimination of the oxazolidinone. Thus, using an isonitrile **9** similar to the Ugi convertible isonitrile **3**, we expected to obtain the *N*-acyloxazolidinones from the Ugi products. Since the C–N bond in the *N*-acyloxazolidinones can be cleaved by several nucleophiles under mild conditions, this protocol would allow the production of numerous analogues.

Here we describe the Ugi 4CC reaction with the novel isonitrile **9** and a convenient procedure for conversion of the Ugi products by cleavage of the *C*-terminal amide bond.



Scheme 1 Ugi 4CC and its limitations

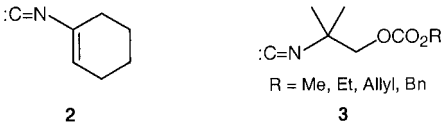
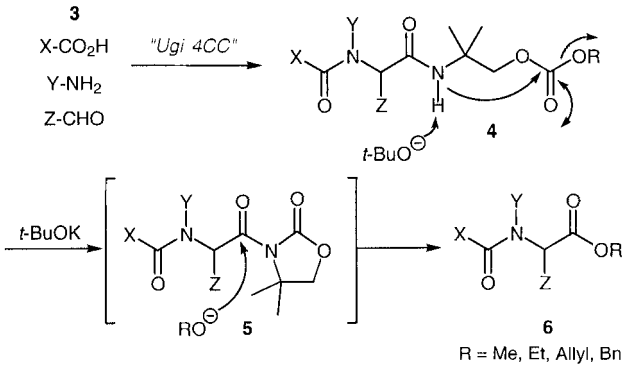


Figure 1 Convertible Isonitriles

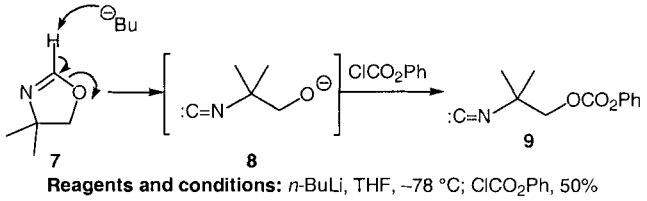


Scheme 2 Ugi approach

Our working hypothesis for the isonitrile **9** is based on the theory that the phenoxide anion would not attack the *N*-acyloxazolidinone of **5**, because of its weak nucleophilicity (pKa = 10). Preparation of the isonitrile **9** was performed according to the Ugi protocol.[6,12] Upon treatment

SYNLETT 2004, No. 1, pp 0041–0044
Advanced online publication: 26.11.2003
DOI: 10.1055/s-2003-43355; Art ID: U21003ST

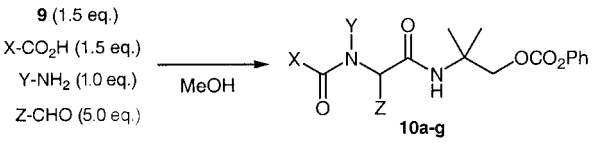
of 4,4-dimethyloxazoline (**7**)[13] with *n*-BuLi, smooth deprotonation and elimination gave the β-isocyanoalkoxide **8**. Subsequent protection of the alkoxide intermediate by phenyl chloroformate afforded the isonitrile **9** (Scheme 3). The isonitrile **9** has the advantage of being odorless and stable under silica gel chromatographic purification.



Scheme 3 Preparation of isonitrile **9**[12]

With the requisite isonitrile **9** in hand, the Ugi 4CC reaction of the combined aromatic and/or aliphatic amines, aldehydes and carboxylic acids was carried out.[14] As shown in Table 1, the 4CC proceeded smoothly to give the desired α-amino amide derivatives **10a**–**g** in almost quantitative yields. In the case of entry 7, a relatively higher temperature was needed for the completion of the reaction. Next, we turned our attention to the transformation of the Ugi products **10a**–**g** to the *N*-acyloxazolidinones **11a**–**g**.[15] After several attempts at cyclization, treatment with *t*-BuOK in THF in the presence of molecular sieves 4 Å (MS 4 Å) gave the best results. As shown in Table 2, the desired cyclization proceeded smoothly to afford the *N*-acyloxazolidinones **11a**–**g** in more than 80% yield. As expected, the nucleophilic attack of the phenoxide anion on the *N*-acyloxazolidinones did not occur. Furthermore, MS 4 Å play a key role in preventing hydrolysis of the starting materials and/or products by moisture.[16]

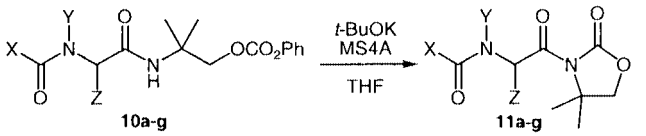
Table 1 Ugi 4CC Reaction with Isonitrile **9**[14]



Entry	X	Y	Z	Temp (°C)	Time (min)	Yield (%)
1	Ph	Bn	*i*-Pr	r.t.	60	91 (**10a**)
2	Ph	Bn	H	r.t.	10	88[a] (**10b**)
3	Ph	Bn	Me	r.t.	10	83 (**10c**)
4	Ph	Bn	Ph	r.t.	60[b]	88 (**10d**)
5	Me	Bn	*i*-Pr	r.t.	60	98 (**10e**)
6	Ph	Ph	*i*-Pr	r.t.	10	99 (**10f**)
7	Ph	Ph	Ph	70	60[b]	89 (**10g**)

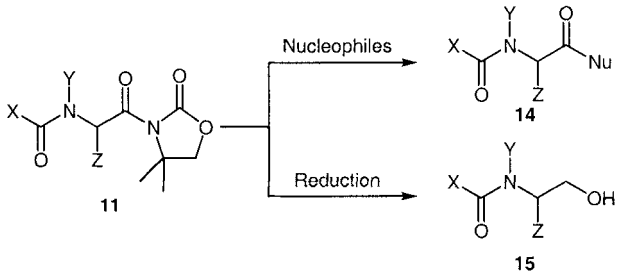
[a] Small amounts of inseparable impurities were detected by ^{1}H NMR;
[b] The starting material remained

Table 2 Formation of Oxazolidinone Rings[15]



Entry	X	Y	Z	Temp (°C)	Time (min)	Yield (%)
1	Ph	Bn	*i*-Pr	0	10	83 (**11a**)
2	Ph	Bn	H	0	10	85 (**11b**)
3	Ph	Bn	Me	0	10	90 (**11c**)
4	Ph	Bn	Ph	0	10	89 (**11d**)
5	Me	Bn	*i*-Pr	0	10	95 (**11e**)
6	Ph	Ph	*i*-Pr	0	10	82 (**11f**)
7	Ph	Ph	Ph	0	10	86 (**11g**)

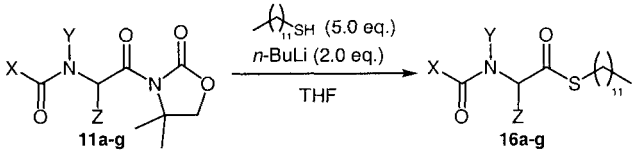
Since the C–N bond in *N*-acyloxazolidinones is activated by two carbonyl groups, cleavage of the amide bonds was accomplished readily by addition of a hetero-nucleophile or via $LiBH_4$ reduction, similar to the Evans oxazolidinones[17–19] (Scheme 4). Among the possible nucleophiles, thiol groups would be attractive, since the thiol esters could be converted into the corresponding aldehydes[20a] or ketones[20b] in the presence of a palladium catalyst. The Pd-mediated reduction by triethylsilane and alkylation with zinc reagents of the thiol esters were developed by our group. The conversion of the *N*-protected α-amino carbonyl compounds proceeded readily under neutral conditions. Recently, we also reported that thiol esters, derived from odorless *n*-dodecanethiol,[21] could be applicable to the Pd-mediated reaction instead of ethanethiol.[22] Thus, upon treatment of the *N*-acyloxazolidinones **11a**–**g** with lithium thiolate generated from *n*-BuLi and *n*-dodecanethiol, the conversion proceeded smoothly to give the *n*-dodecanethiol esters **16a**–**g** (Table 3).[23,24]



Scheme 4 Transformation from *N*-acyloxazolidinones

In conclusion, we have developed a highly efficient, versatile synthetic method for α-amino acid derivatives by means of the Ugi 4CC reaction with a newly developed isonitrile **9**. As summarized in Scheme 5, the choice of the appropriate components, acids (X), amines (Y) and aldehydes (Z) and/or nucleophiles (R) for the *N*-acyl-

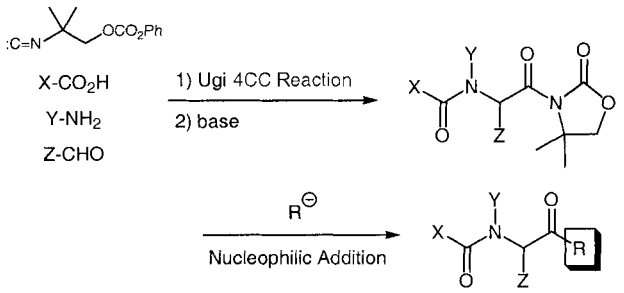
Table 3 Formation of Thiol Esters[23]



Entry	X	Y	Z	Temp (°C)	Time (min)	Yield (%)
1	Ph	Bn	*i*-Pr	0	10	83 (**16a**)
2	Ph	Bn	H	0	10	79 (**16b**)
3	Ph	Bn	Me	0	10	75 (**16c**)
4	Ph	Bn	Ph	0	10	66 (**16d**)
5	Me	Bn	*i*-Pr	0	10	78 (**16e**)
6	Ph	Ph	*i*-Pr	0	10	86 (**16f**)
7	Ph	Ph	Ph	0	10	68 (**16g**)

oxazolidinones and thiol esters would allow us to synthesize a variety of *N*-acylamino acid derivatives.

Further applications of this methodology to the syntheses of a range of peptidomimetic derivatives and/or natural products are under investigation in our laboratories.



Scheme 5

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(10) (a) For the use of *N*-*tert*-butoxycarbonylation to activate amides, see: Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2425. (b) For its application to the Ugi 4CC reaction, see: Hulme, C.; Ma, L.; Cherrier, M.-P.; Romano, J. J.; Morton, G. *Tetrahedron Lett.* **2000**, *41*, 1883.

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(12) **Synthesis of Isonitrile 9:** To a stirred solution of 4,4-dimethyloxazoline (0.997 g, 10.1 mmol) in THF (10 mL) under Ar atmosphere at –78 °C, was added dropwise *n*-BuLi (1.1 M solution in hexane, 9.60 mL, 10.6 mmol) in a duration of 5 min and stirred at same temperature for 1 h followed by dropwise addition of phenyl chloroformate (1.40 mL, 10.7 mmol). After stirring for 5 min, the reaction mixture was warmed to ambient temperature and diluted with Et_2O, and water was added to the mixture. The organic layer was separated and washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, the resulting residue was purified by silica gel chromatography (EtOAc–hexane = 1:9–1:4) to afford 1.10 g of **9** (49.7%). IR (film): 2991, 2136, 1767, 1592, 1496, 1457, 1401, 1378, 1258, 1074, 1024, 970, 879, 835, 775, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.19 (m, 5 H), 4.21 (s, 2 H), 1.53 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 153.1, 150.8, 129.4, 126.1, 120.8, 72.9, 56.1, 25.6. HRMS (FAB): *m*/*z* calcd for $C_{12}H_{13}NO_3$: 219.0895; found: 219.0900.

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(14) **General Procedure for the Ugi 4CC with Isonitrile 9, Synthesis of 10a:** To a stirred solution of isonitrile **9** (223 mg, 1.02 mmol), isobutylaldehyde (0.310 mL, 3.40 mmol), and benzoic acid (128 mg, 1.05 mmol) in MeOH (3.5 mL, 0.19 M) was added dropwise benzylamine (74 μL, 0.68 mmol) within 2 min at ambient temperature. After stirring for 60 min, the solvent was removed under reduced pressure. The resultant crude mixture was purified by silica gel chromatography (EtOAc–hexane = 1:9–1:2) to afford 310 mg of **10a** (91%) as a pale yellow foam. IR (film): 3301, 3063, 2968, 1764, 1680, 1620, 1545, 1496, 1457, 1367, 1263, 1211, 1066, 963, 918, 774, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.05 (m, 15 H), 4.67 (d, *J* = 16 Hz, 1 H), 4.45 (m, 2 H), 4.29 (d, *J* = 11 Hz, 2 H), 2.80 (m, 1 H), 1.36 (m, 6 H), 1.02 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 170.2, 153.6, 151.1, 136.6, 136.5, 129.8, 129.5, 128.5, 128.4, 127.8, 127.7, 126.7, 126.0, 121.0, 76.7, 72.1, 54.0, 52.8, 27.2, 24.3, 23.8, 19.8, 19.5. HRMS (FAB): *m*/*z* calcd for $C_{30}H_{34}N_2O_5$: 502.2468; found: 502.2485.

(15) **General Procedure for the Synthesis of *N*-Acyloxazolidinones, Synthesis of 11a:** To a stirred solution of **10a** (220 mg, 0.44 mmol) in anhyd THF (2.0 mL, 0.22 M) at 0 °C was added freshly activated MS 4 Å (powder, 280 mg), and stirred for 10 min, followed by dropwise addition of 1.0 M *t*-BuOK in *t*-BuOH (0.45 mL, 0.45 mmol) in a duration of 2 min. After stirring for 5 min, 10% aq citric acid was added and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, the resultant crude mixture was purified by silica gel chromatography (EtOAc–hexane = 1:9–1:2) to afford **11a** (149 mg, 83%) as a pale yellow foam. IR (film): 2968, 2360, 1779, 1701, 1646, 1496, 1374, 1305, 1231, 1173, 1089, 1031, 761, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 10 H), 5.63 (m, 1 H), 4.88 (m, 2 H), 3.94 (m, 2 H), 2.43 (m, 1 H), 1.49 (s, 3 H), 1.33 (s, 3 H), 0.93 (d, *J* = 15 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 173.9, 172.3, 152.9, 138.7, 136.7, 129.6, 128.6, 128.3, 128.2, 127.4, 126.8, 126.3, 75.1, 61.0, 29.5, 24.3, 23.8, 19.4, 18.6. HRMS (FAB): *m*/*z* calcd for $C_{24}H_{28}N_2O_4$: 408.2049; found: 408.2033.

(16) In the absence of MS 4 Å, the reaction resulted in low yields, accompanied by the *N*-acylamino alcohols **12** and/or carboxylic acid **13** (Figure 2).

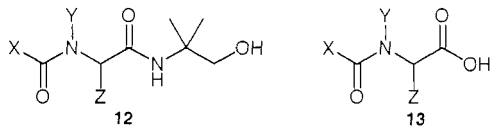

Figure 2

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(23) **General Procedure for the Synthesis of Thiolesters, Synthesis of 16a:** To a solution of *n*-dodecanethiol (0.26 mL, 1.08 mmol) in anhyd THF (2.5 mL) at 0 °C was added dropwise *n*-BuLi (1.0 M solution in hexane, 0.40 mL, 0.40 mmol) for 2 min. After stirring for 5 min, the resulting white suspension was added to a solution of *N*-acyloxazolidinone **11a** (93 mg, 0.23 mmol) in THF (1.5 mL) at 0 °C. After stirring for 10 min, 10% aq citric acid was added and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, the resultant crude mixture was purified by silica gel chromatography (EtOAc–hexane = 1:9–1:2) to afford **16a** (94 mg, 83%) as a white solid. IR(film): 2915, 2854, 1684, 1653, 1457, 1300, 1129, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58–6.98 (m, 10 H), 4.88 (d, *J* = 14 Hz, 1 H), 4.65 (d, *J* = 15 Hz, 1 H), 4.10 (d, *J* = 7.3 Hz, 1 H), 2.77 (t, *J* = 15 Hz, 2 H), 2.43 (m, 1 H), 1.30–1.00 (m, 20 H), 0.88 (t, *J* = 14 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 173.5, 138.1, 136.2, 129.7, 128.5, 128.3, 128.1, 127.8, 127.5, 126.8, 73.5, 62.7, 50.3, 45.8, 31.9, 29.6, 29.5, 29.4, 29.1, 29.0, 22.7, 19.5, 19.1, 14.1. HRMS (FAB): *m*/*z* calcd for $C_{24}H_{28}N_2O_4$: 495.3171; found: 495.3169.

(24) In order to avoid the thiolate addition to the carbonyl group on the oxazolidinone ring, the reaction should be carried out at a temperature lower than 0 °C. Reactions at higher temperature often provided the undesired *N*-acylamino alcohols **12**. This tendency was notably observed in compounds possessing a bulky substituent at the Z-position.