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Nonracemizable Isocyanoacetates for Multicomponent Reactions

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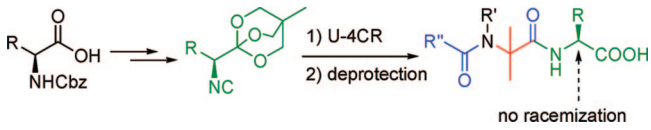

Chiral ortho esters of α-isocyano acids were synthesized from commercially available Cbz-protected α-amino acids. These compounds are stable toward racemization in the Ugi 4CC in contrast to known esters of α-isocyano acids. Applying them in Ugi 4CC with subsequent deprotection gives access to dipeptides with preserved configuration at the C-terminal amino acid.

The Ugi multicomponent reaction (U-MCR) is one of the most important tools for creating substances with high levels of molecular diversity.[1a−c] In particular, U-MCR is used to construct molecules with two amide bonds and, consequently, represents a general efficient method for the synthesis of peptidomimetics.[1d] This method permits the replacement of natural amino acids in biologically relevant peptides with nonproteinogenic derivatives that may influence their properties dramatically.[1e,f] This promising approach has attracted attention for years, but it still needs improvement in many aspects. α-Isocyano esters (isocyanoacetates) **1** easily accessible from α-amino acids are the simplest isocyanide derivatives of α-amino acids. These building blocks have been used to date in U-MCR to introduce a C-terminal amino acid into the structure of desired peptide **2** (Scheme 1). However, there are some disadvantages of the method. Reactivity of **1** is lowered due to strong electron-withdrawing effects of the carboxyl group (especially in reactions with ketones). Isocyano and carboxyl groups together increase significantly the acidity of the α-hydrogen atom; hence, side reactions involving this site of the molecule are possible.[2]

No data for acidity of isocyanoacetates are given in literature; however, its pK_a can be estimated in the range of 9−11.[3] But their main disadvantage is racemization occurring easily under conditions of U-4CR due to basicity of the amine.[4] Also, special conditions are required for the synthesis of isocyanides **1** in optically pure form.[5]

We decided to develop another type of α-amino acid isocyanides for the synthesis of peptides by U-4CR, which would be configurationally stable in basic conditions. We assumed that transformation of a carboxyl group into an OBO-ester (4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl derivatives) would avoid all aforementioned problems and open a way to protected peptides **4** with preserved configuration of the C-terminal amino acid. Furthermore, reaction with ortho esters opens a way to peptides with an OBO-protective group, which is stable to nucleophiles and bases and can be easily removed under mild conditions without racemization.[6] We report herein large-scale oriented synthesis of new chiral OBO-esters of α-isocyano acids **3** and our studies on their stability toward racemization and behavior in the Ugi reaction.

OBO-esters are synthesized by BF_3-catalyzed rearrangement of the corresponding 3-methyl-3-(hydroxymethyl)oxetane esters.[7] For this rearrangement to take place, amino group has to be protected. However, under reaction conditions, *N*-formylglycine ester gave only insoluble precipitate instead of the desired OBO-ester, the immediate precursor for the corresponding isocyanide. A possible reason is Lewis acid/base reaction of the BF_3 with the amide moiety.[8] Experiments with other Lewis and Brönsted acids ($AlCl_3$, $TiCl_4$, $Yb(OTf)_3$, CF_3COOH, CF_3SO_3H, H_2SO_4) were unsuccessful. Therefore, we used Cbz derivatives because of their high efficiency of introduction/removal processes and availability of the corresponding Cbz-amino acids. Also, the synthesis of the OBO-ester of glycine **11a** via the Cbz derivative has been recently reported.[9]

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(2) Some isocyanoacetates are widely used in organic synthesis, where enhanced CH-acidity of them plays key role; see, for example: (a) Suzuki, M.; Nunami, K.; Moriya, T.; Matsumoto, K.; Yoneda, N *J. Org. Chem.* **1978**, *43*, 4933–4935. (b) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; A. Orru, R. V *Org. Lett.* **2003**, *5*, 3759–3762. (c) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406. (d) Schröder, R.; Schöllkopf, U.; Blume, E.; Hoppe, I. *Liebigs. Ann. Chem.* **1975**, *3*, 533–546.

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(4) Bayer, T.; Riemer, C.; Kessler, H. *J. Peptide Sci.* **2001**, *7*, 250–261. However, the enantiomerically enriched α-isocyano acetamide is known to undergo the oxidative Ugi reaction without significant racemization, but amides are weaker CH-acids than esters; see: Ngouansavanh, T.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5775.

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(6) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021–5030.

(7) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571–5574.

(8) Herdeis, C.; Kelm, B. *Tetrahedron* **2003**, *59*, 217.

(9) Raghavan, B.; Johnson, R. L. *J. Org. Chem.* **2006**, *71* (5), 2151–2154.

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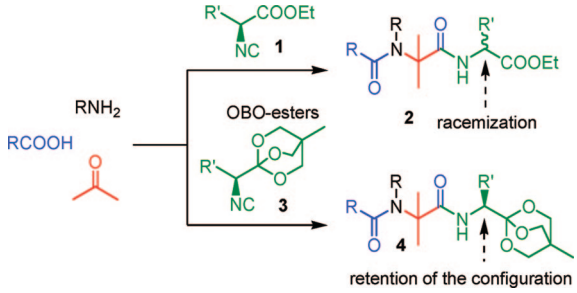
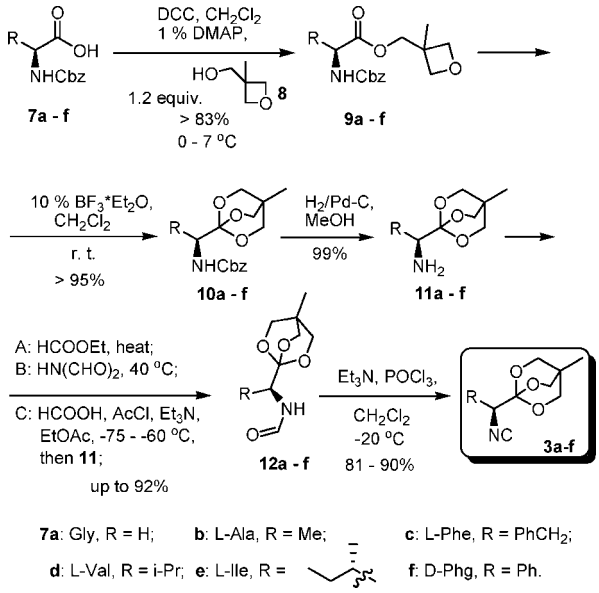
SCHEME 1. Ugi Reaction with α-Isocyanoesters



SCHEME 2. Synthesis of OBO-esters of α-Isocyano Acids 3a−f



The esterification of **7a−f** was accomplished by 3-methyl-3-(hydroxymethyl)oxetane **8** using the DCC reagent to afford the esters **9a−f** in high yield (Scheme 2). The latter were treated with 0.1 equiv of $BF_3 \cdot Et_2O$ to give OBO-products **10a−f** quantitatively. Smooth removal of the Cbz group was carried out by hydrogenolysis. At the next step, it was necessary to elaborate an efficient method of formylation of amines **11a−f** in nonacidic conditions to avoid cleavage of the OBO-group. The best reagent was found to be acetic-formic anhydride (AFA) generated in situ.[10] Alternatively, ethyl formate can be used, but for unhindered substrates **11a−c** only. Diformamide $HN(CHO)_2$ can be used as reactive and neutral formylating reagent,[11] but it has some disadvantages concerning isolation and purification of the products. The final dehydration of formamides **12a−f** was performed by a classic method using $POCl_3/Et_3N$ in CH_2Cl_2 at −20 to −15 °C.[12] The desired isocyanides **3a−f** were obtained in high yield and in high optical purity (vide infra). It is noteworthy that all isocyanides **3a−f** are stable solid odorless compounds in contrast to their low molecular weight analogues.

XRD analysis of **3e**, prepared from L-isoleucine (containing two stereocenters), showed the relative configuration of stereocenters to be the same as in initial amino acid.[13] The configuration at the C3 atom could not be changed; this means that no racemization at C2 atom occurred during all steps of synthesis.

TABLE 1. Investigation of Stability of 3c−f toward Racemization

N	isocyanide	conditions of racemization (rt)	$[\alpha]_D$
1	Ile **3e**	starting sample	−13.0
2	Ile **3e**	MeONa, MeOH, 3 h	−12.9
3	Ile **3e**	1.5 M MeONa, MeOH, 48 h	−13.0
4	Ile **3e**	0.13 M *t*-BuOK, THF, 3 h	−12.0
5	Phe **3c**	starting sample	−50.8
6	Phe **3c**	MeONa, MeOH, CH_2Cl_2, overnight	−50.5
7	Phe **3c**	1 M MeONa, MeOH, CH_2Cl_2, 48 h	−50.1
8	Phe **3c**	0.1 M DBU, CH_2Cl_2, 48 h	−50.6
9	Val **3d**	starting sample	−13.8
10	Val **3d**	0.13 M *t*-BuOK, THF, 1 h	−13.2
11	Val **3d**	0.13 M *t*-BuOK, THF, 2 h	−12.4
12	Val **3d**	0.26 M *t*-BuOK, THF, 5 h	−9.0
13	Val **3d**	0.26 M *t*-BuOK, THF, 41 h	−0.9
14	Phg **3f**	starting sample	−33.8
15	Phg **3f**	0.1 M DBU, CH_2Cl_2, 85 h	−30.5
16	Phg **3f**	1.3 M MeONa, MeOH, CH_2Cl_2, 72 h	0
17	Phg **3f**	0.13 M *t*-BuOK, THF, 40 min	0

The stability of the isocyanides toward racemization was studied by determination of optical rotary power before and after treatment with MeONa/MeOH, DBU/CH_2Cl_2 and *t*-BuOK/THF solutions (Table 1). It was shown that isocyanides **3c−e** are stable toward racemization in DBU or MeONa solutions at rt during several days but racemize slowly in *t*-BuOK solution (almost full racemization of **3d** was achieved in 41 h, entry 13). The most CH-acidic isocyanide **3f** suffers slow racemization in DBU and MeONa solutions and fast racemization in *t*-BuOK solution (in 40 min, entry 17).

In the case of **3c**, decomposition of starting material in *t*-BuOK solution was observed. It was found that **3c** eliminates slowly HCN to give *trans*-alkene Ph-CH=CH-OBO (**13**) exclusively.[14]

In addition, determination of optical purity was achieved by carrying out Ugi reactions with chiral amine **20** (Table 2). In ^1H and ^{13}C NMR spectra of the products **25−28** (entries 5−8), only one set of signals was observed, indicating formation of only one diastereomer (>99% de). Only in the case of **28** a minor diastereomer was observed, indicating dr 94:6. In contrast, ^1H and ^{13}C NMR spectra of **30** and **31**, prepared from racemic isocyanides **3d** and **3f**, show two sets of signals, indicating formation of 1:1 mixture of the diastereomers (entries 10 and 11). The Ugi reactions were run with different substrates to study synthetic utility of **3a−f** (Table 2). In all cases, the corresponding protected dipeptides were obtained in moderate to high yields. It is noteworthy that the presence of two bulky substituents in **3d**,**e** did not have a significant influence on the reactivity (entries 4, 6, 7, and 10). Reduced yields for isocyanide **3f** can be attributed to it is poor solubility in methanol (entries 8 and 11).

Removal of the OBO group was achieved in a simple two-step, one-pot procedure (Scheme 3) in quantitative yield. The rate of the saponification stage slightly depends on the nature of a C-terminal acid. Subsequent acidification and extraction

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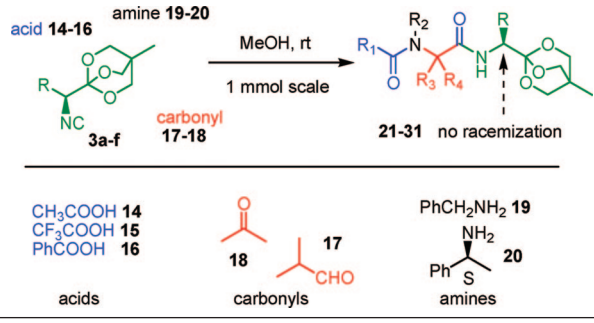
(11) The synthesis of diformamide:(a) Allenstein, E.; Beyl, V *Chem. Ber.* **1967**, *100*, 3551–3563. Formylations by diformamide: (b) Kashima, C.; Arao, H.; Hibi, S.; Omote, Y *Tetrahedron Lett.* **1989**, *30*, 1561–1562.

(12) Ugi, I.; Meyr, R. *Angew. Chem.* **1958**, *70*, 667–718.

(13) CCDC 694486 contains the supplementary crystallographic data for **3e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, www.ccdc.cam.ac.uk/data_request/cif.

(14) A few examples of β-elimination of HCN from isocyanides are known in literature; see, for example: Jones, B. A.; Varma, M.; Stirling, C. J. M. *J. Am. Chem. Soc.* **1986**, *108*, 3153–3154.

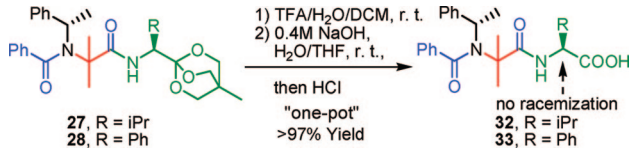
TABLE 2. Ugi Reactions with Isocyanides 3a−f



N	isocyanide	acid	C=O	amine	product	yield[a]
1	Gly **3a**	**14**	**17**	**19**	**21**	80
2	Gly **3a**	**15**	**17**	**19**	**22**	68
3	Ala **3b**	**14**	**18**	**20**	**23**	66
4	Ile **3e**	**14**	**18**	**19**	**24**	70
5	Ala **3b**	**16**	**18**	**20**	**25**	60
6	Ile **3e**				**26**	46
7	Val **3d**				**27**	49
8	Phg **3f**				**28**	36
9	Gly **3a**				**29**	54
10	Val **3d**rac				**30**[b]	47
11	Phg **3f**rac				**31**[b]	37

[a] Isolated yield (%). [b] Racemic isocyanide was used.

SCHEME 3. Removal of the OBO Group



into ethyl acetate leads to a pure acid without need of further purification. No racemization was observed in the case of L-valine derivative **32** and a maximum 8% of racemized product was determined in the D-phenylglicyne derivative **33** according to NMR spectra. This racemization degree is attributed to the most racemization labile scheme starting from the amino acid **7f** and represents the limit of racemization observed in this study.

In conclusion, we have elaborated new chiral isocyanide derivatives of α-amino acids **3**, which are stable against racemization under basic conditions. They were synthesized from corresponding Cbz-protected α-amino acids in high common yields by simple and scalable procedures. A series of Ugi products were prepared under standard conditions demonstrating high synthetic potential of **3** for peptide preparation. In contrast to isocyanoacetates **1**, the use of isocyanides **3** allows to synthesize protected peptides **4** with preserved configuration of C-terminal amino acid. Removal of the OBO-group in peptides **4** was achieved in high yield under aforementioned conditions and was shown to be a racemization-free process as well.

Experimental Section

General Procedure 1. 3-Methyl-3-oxetanemethanol Esters of Cbz-α-amino Acids 9a−f. The acid **7a−f** (1 equiv.) was added portionwise to a stirred solution of DCC (1.01 equiv), 3-methyl-3-oxetanemethanol (1.2 equiv), and DMAP (0.01 equiv) in dry methylene chloride at 0−5 °C. The reaction mixture was additionally stirred for 30−60 min (TLC analysis, EA-hexanes 1:1 or 1:2). Then the precipitate of dicyclohexylurea (DCU) was filtered off and washed with methylene chloride. The filtrate was washed with water, 0.01 N HCl, and brine, dried over Na_2SO_4, and concentrated in vacuo. The muddy residue was diluted with a minimum amount of ethyl acetate, filtered through a short SiO_2 column, and concentrated in vacuo to give the crude ester as a solid **9f** or clear oil **9a−d** which was used further without purification (with the exception of **9d**,**e**).

Note: Only in cases of valine and isoleucine derivatives **9d**,**e**, significant amount of byproducts were formed and the products were purified by column chromatography, but small amounts of DCU still remained. In all cases, a small amount of DCU is inseparable by column chromatography and can be filtered off from the concentrated solution in ethyl acetate.

(3-Methyloxetan-3-yl)methyl (2*R*)-{[(benzyloxy)-carbonyl]amino}(phenyl)acetate (Cbz-Phg-Oxe, 9f). Reaction between **7f** (12.3 g, 0.0431 mol), **8** (5.28 g, 0.0518 mol), DMAP (0.05 g, 0.4 mmol), and 9.07 g (0.0440 mol) of DCC in 70 mL of dry methylene chloride, according to General Procedure 1: crude yield ∼100%; white solid; $[\alpha]^{25}_D$ −75.9 (*c* 2.0, CH_2Cl_2); IR (Nujol, cm^{-1}) 3345 (NH), 1740 (COO), 1695 (CONH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.30 (m, 10H), 5.92 (br d, 1H), 5.43 (d, 1H, J = 7.3 Hz), 5.17−5.09 (2d, 2H, J = 12.4 Hz), 4.37 (2d, 2H, J = 6.1 Hz), 4.28 (2d, 2H, J = 6.1 Hz), 4.23 (2d, 2H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 155.5, 136.5, 136.2, 129.0, 128.7, 128.5, 128.23, 128.19, 127.08, 79.30, 79.20, 69.8, 67.4, 58.1, 39.1, 20.8. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28. Found: C, 67.93; H, 6.21.

General Procedure 2. OBO-esters of Cbz-α-amino Acids 10a−f. To 0.4 M solution of **9a−f** in dry methylene chloride was added 10 mol % of boron trifluoride etherate. After air had been pumped out, the reaction flask was closed and the mixture was stirred at ambient temperature. After 4−6 h, a TLC analysis (EA−hexanes 1:2, or 1:1 for **10a**,**b**) indicated complete conversion of the starting material. Then, Et_3N (1.5 equiv to BF_3) was added, and the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate, washed with diluted aqueous K_2CO_3, and brine, and dried over Na_2SO_4 and evaporated.

Note: this reaction proceeds in quantitative yield without formation of byproducts. OBO-esters **10a−f** are stable crystalline compounds and may be purified easily by recrystallization from methanol/hexanes or ethyl acetate/hexanes but may be used without purification as well.

General Procedure 3. OBO-esters of α-Amino Acids 11a−f. 10a−f, the catalyst (10% or 5% Pd on carbon), and methanol were loaded in an 150 mL autoclave with magnetic stirrer. After this, hydrogen was pumped up to 30 atm, and the reaction mixture was stirred at ambient temperature until the pressure started to drop and complete conversion by TLC (eluent EA) was observed. Then reaction mixture was filtered through Celite, and the slightly muddy yellow filtrate was concentrated in vacuo to give an amine.

Note: The rate of reaction depends on purity of starting material. When recrystallized material was used, the hydrogenation was complete after 30 min at 30 atm. But when the material was used without purification, the rate of reaction was lower; in some cases, an additional portion of catalyst was added to the poisoned one to achieve a full conversion.

General Procedure 4. Method C. This represents a modified procedure.[10] To a three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel were added 60 mL of dry ethyl acetate, 1.3 mL (1.2 equiv) of formic acid, and 2.38 mL (1.15 equiv) of acetyl chloride. Dry triethylamine (10.1 mL, 2.5 equiv) was added dropwise with stirring at such rate to allow the temperature to be kept at −75 to −60 °C. A white precipitate formed instantly in an exothermic reaction. The temperature was allowed to rise while 5.02 g of **Ala-OBO 11b** was added dropwise. Then the reaction mixture was stirred for 5 min at ∼−40 to −20 °C, and TLC control (eluent EA) showed the reaction was already complete. The precipitate was filtered off and washed with portions of ethyl acetate or acetone. The filtrate was concentrated in vacuo, diluted with methylene chloride, and washed

with concentrated K_2CO_3 + a little of KOH (aqueous phase should remain alkaline) and brine. The organic phase was dried over Na_2SO_4 and evaporated.

(1*S*)-1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)ethylformamide (OHCNH-Ala-OBO, 12b): yield 90% (method C); white solid; mp 100−102 °C; R_f (EA) 0.3, (CH_2Cl_2−MeOH 15:1) 0.57; $[\alpha]^{25}_D$ −54.3 (*c* 2.0, CH_2Cl_2); IR (Nujol, cm^{-1}) 3270 (NH), 1660 (CONH); mixture of rotamers 2.08:1; major (trans-) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1H, 1.26 Hz), 5.79 (br. s, 1H), 4.27 (dq, 1H, J = 6.8, 8.5 Hz), 3.92 (s, 6H), 1.18 (d, 3H, J = 6.8 Hz), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 108.2, 72.7, 47.7, 30.5, 15.5, 14.3; minor (cis-) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 1H, 12 Hz), 5.54 (bt, 1H), 3.90 (s, 6H), 3.54 (dq, 1H, J = 6.8, 9.7 Hz), 1.23 (d, 3H, J = 6.8 Hz), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 107.7, 72.7, 51.9, 30.7, 14.2. Anal. Calcd for $C_9H_{15}NO_4$: C, 54.52; H, 7.51. Found: C, 54.86; H, 7.63.

OBO-esters of α-Isocyano Acids 3a−f. General Procedure 5. To a stirred solution of **12a−f** and 2.5 equiv of dry Et_3N in dry methylene chloride (concn 0.06 mol **12a−f** per 100 mL of CH_2Cl_2) was added 1.1 equiv of $POCl_3$ at −20 to −15 °C (exothermic reaction). The reaction mixture was stirred for an additional 10 min; a small amount of $POCl_3$ was added for complete conversion (TLC control, eluent EA). After this, the reaction mixture was poured into a cooled (!) to 0 °C solution of 5 equiv of KOH in water (NaOH forms precipitate due to low solubility of Na_2HPO_4 in water) and stirred for 10 min. The organic phase was washed with water and brine, dried over Na_2SO_4, and evaporated. The residue was diluted in ethyl acetate and filtered through short SiO_2 column. Evaporation of the solvent gives slightly yellow or orange but almost pure isocyanides as crystalline solids. They may be easily purified by column chromatography (eluent EA−hexanes 1:1). **3c**,**f** may be easily recrystallized from methanol or ethyl acetate.

(*R*)-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)(phenyl)methyl isocyanide (CN-Phg-OBO, 3f): yield 90%; white solid; mp 172−174 °C; $[\alpha]^{25}_D$ −33.8 (*c* 2.0, CH_2Cl_2); IR (Nujol, cm^{-1}) 2170, 745, 713 (Ph); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.37 (m, 5H), 4.80 (s, 1H), 3.94 (s, 6H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (b), 132.3, 128.8, 128.5 (2C), 128.1 (2C), 107.0, 73.1, 62.1 (b), 31.0, 14.2. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16. Found: C, 68.50; H, 6.20.

General Procedure 6. Ugi Reactions with Isocyanides 3a−f. A solution of carbonyl compound (1 mmol for **17**, 1.5−2 mmol for **18**), amine **19** or **20** (1 mmol), acid **14−16** (1 mmol), and isocyanide **3a−f** (1 mmol) in 1 mL of methanol was kept for 2−4 days, and then it was evaporated with SiO_2 (a few drops of Et_3N may be added to prevent opening of ortho-ester, but not required) and chromatographed on silica gel, using gradient elution EA−hexanes 1:1 → EA (5 × 2 cm SiO_2 column is sufficient in most cases, eluent change immediately after upper fraction).

Compound 21: yield 80%; white solid; mp 169−170 °C; IR (Nujol, cm^{-1}) 3320 (NH), 1650 (CONH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.27 (t, 2H), 7.24−7.20 (t, 1H), 7.17−7.15 (d, 2H), 6.54 (br s, 1H), 4.76 and 4.54 (2d, 2H, J = 17.4 Hz), 4.60 (d, 1H, J = 10.9 Hz), 3.92 (s, 6H), 3.44 and 3.28 (2dd, 2H, J = 5, 13 Hz), 2.39 (m, 1H), 2.01 (s, 3H), 0.95 (d, 3H), 0.84 (d, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 169.9, 137.6, 128.6, 127.0, 126.2, 107.0, 72.7, 64.5, 49.4, 43.7, 30.6, 27.1, 22.5, 19.6, 18.9, 14.3. Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74. Found: C, 63.63; H, 7.27.

General Procedure for the Removal of the OBO Group. To a solution of compound **27** (0.2 g, 0.4 mmol) in 4 mL of methylene chloride were added 0.025 mL of TFA and 0.1 mL of H_2O. The reaction mixture was stirred at rt for 30 min (TLC control: EA) and evaporated. The oily residue was dissolved in 1 mL of THF, and then 3 mL of H_2O and 0.08 g (2 mmol) of NaOH were added. The two-phase mixture was stirred at rt for 1 h for complete hydrolysis and became homogeneous (TLC control: CH_2Cl_2−MeOH 10:1).[15] Then the solution was diluted with 15 mL of H_2O, acidified with concd HCl to pH ∼1, and extracted with ethyl acetate (2 × 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated to afford 0.166 g (98%) of pure acid **32** as a white solid.

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Supporting Information Available: Other experimental procedures, compound characterization, copies of NMR ^{1}H and ^{13}C spectra for all new compounds, and crystallographic data for **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The saponification of **28** under the same conditions required only 30 min to complete.