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Multicomponent Reactions of Cyclobutanones

Michael C. Pirrung* and Jianmei Wang

Department of Chemistry, University of California, Riverside, California 92521-0403

michael.pirrung@ucr.edu

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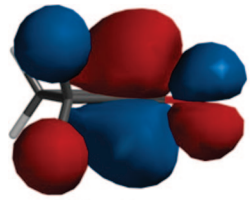
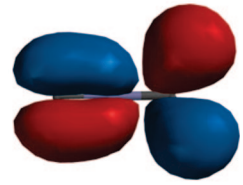


LUMO cyclobutanone



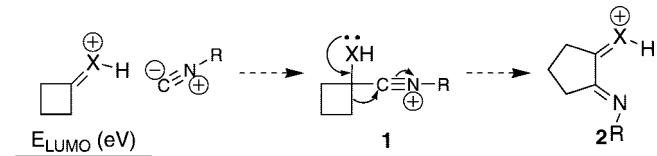
HOMO methyl isonitrile

Cyclobutanones are essentially unknown as reactants in isonitrile-based multicomponent reactions. Ugi reactions of cyclobutanone and Passerini reactions of tetramethylcyclobutane-1,3-dione have been performed in this work. These reactions are significantly enhanced by being conducted in water, a subject of recent interest whose basis is still in question but whose effects are beyond doubt. The Ugi reaction of cyclobutanone has been used in a brief synthesis of an aspartame analogue.

Introduction

Isonitrile-based multicomponent reactions have a long history in organic synthesis.[1] A wide variety of reactants participate in the three-component Passerini reaction (acid, isonitrile, carbonyl) and four-component Ugi reaction (acid, isonitrile, carbonyl, amine), yet there is miniscule record of the use of cyclobutanones in such reactions.[2] There are two perspectives on the potential reactivity of a cyclobutanone in such processes. As is well-known,[3] nucleophilic addition to cyclobutanones is faster than for most other ketones. Such reactions benefit from relief of strain in converting an sp2-hybridized carbon in a small ring to a sp3-hybridized carbon. From a more modern perspective, the LUMO energy of cyclobutanone is lower than that of most other ketones (for example, 0.3 eV less than the cyclohexanone LUMO[4]), increasing interactions between it and the isonitrile HOMO in the transition state for the addition step. As the protonated carbonyl (or imine) is the actual electrophile in the multicomponent reactions of interest here, it seemed worthwhile to consider the LUMO energies of those specific

SCHEME 1



E_{LUMO} (eV)	
X=O	-3.42
X=NMe	-1.98

reactive intermediates, comparing those derived from cyclobutanone to those derived from a prototype reactant, cyclohexanone. These LUMO energies were calculated using the RHF/6-31G* method in Spartan. Protonated cyclobutanone has a LUMO energy (Scheme 1) 7.48 eV below that of cyclobutanone, whereas protonated cyclohexanone has a LUMO energy 7.30 eV below that of cyclohexanone. Not only does cyclobutanone have a lower LUMO energy to begin with, upon protonation its LUMO energy decreases more than does cyclohexanone's, leading to a nearly 0.5 eV lower LUMO energy for protonated cyclobutanone. These considerations project greater reactivity of cyclobutanones in the Passerini reaction. The protonated methyl imine of cyclobutanone has a LUMO energy (Scheme 1) 6.05 eV below that of cyclobutanone, whereas the protonated methyl imine of cyclohexanone has a LUMO energy 5.98 eV below that of cyclohexanone. Consideration of the FMO interactions projects smaller differences in reactivity between

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(2) Sorensen, B.; Rohde, J.; Wang, J.; Fung, S.; Monzon, K.; Chiou, W.; Pan, L.; Deng, X.; Stolarik, D.; Frevert, E. U.; Jacobson, P.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5958–5962.
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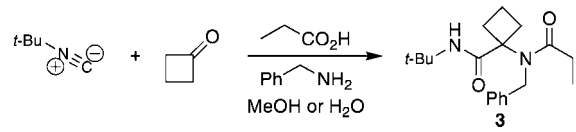
cyclobutanone and cyclohexanone in the Ugi reaction. On the other hand, cyclobutanone might be expected to react poorly in the Ugi reaction owing to the need to generate a cyclobutanone imine by elimination of water from a tetrahedral intermediate. Converting an sp3-hybridized carbon to an sp2-hybridized carbon in a small ring could hinder this step. However, the sparse information available on the rate-limiting step in the multistep mechanisms for Passerini and Ugi reactions makes projection of the effectiveness of cyclobutanones in multicomponent reactions difficult. Rate laws have been reported for both the Passerini[5] and Ugi[6] reactions, but the quality of the data and the kinetic mechanisms proposed in these studies are still open to question.

We considered another potential reason for the lack of past reports on isonitrile-based multicomponent reactions of cyclobutanones: that they follow an unusual reaction course that did not allow the product(s) to be recognized. Shown in Scheme 1 is a hypothetical reaction that does not incorporate the acidic reagent into the product. The addition of an isonitrile to a protonated cyclobutanone carbonyl or imine would give nitrilium ion **1**, as in traditional mechanisms. Since this intermediate has an electrophilic center adjacent to a strained cyclobutane bond, ring expansion (assisted by the unshared electron pair on the heteroatom X, in a process similar to a pinacol rearrangement) to **2** might be projected. Following deprotonation, cyclopentane-1,2-dione monoimines or diimines could be formed. Such compounds are not well-known, and their formation would represent a novel product type. However, contrary to this hypothesis, we report here that two prototype cyclobutanones participate effectively in Passerini and Ugi reactions. The latter was used in the synthesis of a sweet dipeptide based on 1-aminocyclobutanecarboxylic acid.

Results

Because the products of the putative ring-expansion process do not incorporate an acid reactant, while an acid is required for the Ugi and Passerini reactions, we thought that ring expansion might be promoted by omitting acid completely. When cyclobutanone, benzylamine, and *tert*-butyl isocyanide are combined in methanol at room temperature, there is no reaction. Thinking that acid might be necessary to catalyze initial imine formation or promote addition of the isonitrile to the imine, 10 mol % of propionic acid was added. However, the only product observed (in 8% yield) is simply the Ugi product **3**. When 1 equiv of propionic acid was used in this reaction, it was complete after 24 h and **3** was obtained in 84% yield. When the non-nucleophilic acid HBF_4 was used, there was no reaction. Past work in our laboratory has shown that multicomponent reactions can be significantly accelerated by performing them in water[7] and that reactions can be observed when performed in water that have no counterpart when conducted in organic solvents.[8] We therefore examined this reaction in water, but it gives only Ugi product **3** in the same 84% yield as in methanol.

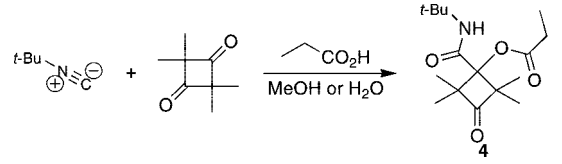
Another commercially available cyclobutanone, tetramethylcyclobutane-1,3-dione, was selected for study, reasoning that its increased ring strain (two sp2-hybridized carbons in a small ring) and migratory aptitude (tertiary migrating carbon) might



(1)

3

facilitate ring expansion. A similar ring expansion of this compound is also known.[9] However, reaction of tetramethylcyclobutane-1,3-dione, 4-methoxybenzylamine, *tert*-butyl isocyanide, and propionic acid in methanol or water gave neither a ring-expansion product nor an Ugi product. Rather, the Passerini product **4** is obtained in low yield (12%) in water, and a complex reaction mixture is obtained in methanol. The observation of Passerini side products in Ugi reactions is fairly common and reflects a slow imine formation step that does not compete with direct nucleophilic addition of the isonitrile to the protonated carbonyl. When 4-methoxybenzylamine was omitted and the reaction was performed as a straight Passerini reaction in methanol, with 2 equiv of isonitrile and acid, **4** could be obtained in low yield (12%), and reactants were still detectable by GC after 2 d.



(2)

4

Because of our past experience in promoting multicomponent reactions by conducting them in water, we aimed to make the synthetically useless Passerini reaction of tetramethylcyclobutane-1,3-dione with propionic acid more practical by performing it in water and by using other acids. Some of these reactions were also examined in methanol. Recent work from our laboratory has suggested that reactions performed in water can be affected by the hydrophobicity of the reactants.[10] As a simple and accessible measure of reactant hydrophobicity, we use the log of the octanol/water partition coefficient or log *P*, which is available for a wide variety of organic compounds, either from compilation or calculation. We have observed that reactions that experience a significant benefit from performing them in water typically have reactant log*P*'s in the range of 1−2. Because the log *P* of propionic acid is 0.35, we considered enhancing the Passerini reaction of tetramethylcyclobutane-1,3-dione (log $P = 1.69$) by using more hydrophobic acid components. The log*P*'s of the five carboxylic acids studied, cyclohexanecarboxylic, 3,3-dimethylacrylic, pivalic, adamantanecarboxylic, and (adamantane)acetic, are given in Table 1 and range from 0.92 to 2.37. *tert*-Butyl isonitrile (log $P = 0.7$) was used in all reactions (2 equiv). We have also observed that reactions in water are frequently dependent on the method of mixing, attesting to their heterogeneous character.[10] All reactions in this study were performed with mixing by wrist-action shaking, which we often find to be most efficient. These reactions were performed at a ketone concentration of 0.1 M, at which all were heterogeneous. For reactants with a low melting point, such as pivalic or cyclohexanecarboxylic acid, the reaction mixture appears cloudy, while for those with a high melting point, such as the adamantanes, solid can be clearly observed. The outcomes

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(7) (a) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444. (b) Pirrung, M. C.; Sarma, K. D. *Tetrahedron* **2005**, *61*, 11456.
(8) Pirrung, M. C.; Das Sarma, K. *Synlett* **2004**, 1425–1427.
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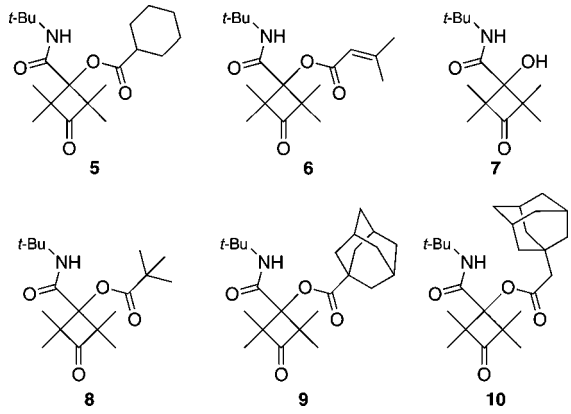
(10) Pirrung, M. C.; Das Sarma, K.; Wang, J. *J. Org. Chem.* **2008**, *73*, 8723.

TABLE 1. Passerini Reactions of Tetramethylcyclobutane-1, 3-dione, *tert*-Butylisonitrile, and Carboxylic Acids RCO_2H

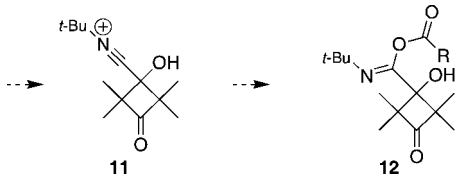
acid R group	acid log P	solvent	acid (equiv)	time (d)	product	yield (%)	yield of **7** (%)
cyclohexyl	1.67	MeOH	2	4	**5**	40	0
cyclohexyl	1.67	H_2O	2	3	**5**	85	0
2-methylprop-1-enyl	0.92	MeOH	2	4	**6**	13	0
2-methylprop-1-enyl	0.92	H_2O	2	3	**6**	31	50
tert-butyl	1.62	H_2O	2	5	**8**	20	39
tert-butyl	1.62	H_2O	5	5	**8**	21	44
tert-butyl	1.62	H_2O	10	5	**8**	30	34
adamantyl	2.37	H_2O	2	5	**9**	60	12
(adamantyl)methyl	2.31	H_2O	2	5	**10**	98	0

CHART 1



of all of these reactions are summarized in Table 1, and their Passerini products are given in Chart 1.

The Passerini reaction of tetramethylcyclobutane-1,3-dione and *tert*-butyl isonitrile with cyclohexanecarboxylic acid in methanol gives the desired product **5** in 40% yield, with reactants still being detected by TLC after 4 d. In water, the reaction is complete after 3 d and the product is obtained in 85% yield. The theory that the Passerini reaction could be enhanced with more hydrophobic acid reactants in water was confirmed. Reaction with 3,3-dimethylacrylic acid in methanol gives **6** in only low yield after 4 d. In water, the reaction is complete after 3 d and the product **6** is obtained in modest yield. The dominant product of this reaction is compound **7**, which is an abnormal Passerini reaction product. We envision this compound arising in one of two ways (eq 3). Intermediate nitrilium ion **11** could undergo direct reaction with water to give the α-hydroxyamide **7**. Alternatively, if **11** instead reacts with the carboxylate to give the imidic anhydride **12**, it might still be hydrolyzed by water intermolecularly rather than undergoing an intramolecular acyl-transfer reaction to give **6**. Data on other carboxylic acids discussed below may bear on the pathway that is followed.



(3)

Reaction with pivalic acid is very slow in methanol and incomplete after 9 d, whereas reaction in water is complete after 5 d. When standard conditions are used with 2 equiv of acid, **8** is still the minor product, and **7** is obtained in 39% yield. To see if the ratio of the Passerini product to the side product could be increased by using more acid, speeding addition to **11**, reactions with 5 and 10 equiv of pivalic acid were also conducted in water. When 5 equiv of acid is used, the reaction affords the two products in a similar ratio. When 10 equiv of acid is used, the ratio of the Passerini product **8** to the hydrolysis product **7** is slightly increased to around 1:1. Reaction with adamantane-1-carboxylic acid, a more hydrophobic carboxylic acid, is very slow in methanol and incomplete after 9 d. In water, the reaction is complete after 5 d. The Passerini product **9** is obtained in 60% yield, and the side product **7** is obtained in 12% yield. The reaction with (1-adamantane)acetic acid in methanol is incomplete after 9 d. The reaction in water is complete after 5 d, and the Passerini product **10** is obtained in almost quantitative yield.

As an example of the utility of the Ugi reaction of cyclobutanone, we used this process as the key step in a synthesis of a simple dipeptide. Since the discovery of aspartame as a peptide sweetener,[11] structure−taste studies have shown that the aspartic acid residue is absolutely essential for sweetness.[11] However, the *C*-terminal residue can vary significantly. Studies have shown that aspartic dipeptides derived from amino acids with small (three- to five-membered) cycloalkanes are sweet, whereas those with larger rings are not.[12] Aspartyl-α-aminocyclobutanecarboxylic acid methyl ester has been reported as a sweet dipeptide by Goodman. His five-step synthesis uses cyclobutanone as the starting material and pursues a classical approach based on the Bucherer−Bergs reaction and traditional peptide couplings, affording the target in 8% overall yield.

Recognizing the potential of the Ugi reaction of cyclobutanone to assemble the full skeleton of this dipeptide, we required an isonitrile whose Ugi product (an amide) could be readily converted to the methyl ester. Many solutions to the problem of so-called convertible isonitriles have been offered,[13] including one from our own laboratory.[14] Several of these were tested in Ugi reactions with cyclobutanone, but most often their reactivity was poor and the Ugi product was obtained in only modest yield. We find wide variance in the reactivity of the reported convertible isonitriles, with the most reactive in this case being 1-isocyanocyclohexene. The relative nucleophilicity of isonitriles has been recently investigated, with *tert*-butyl isonitrile found to be the most nucleophilic among a limited set of five isonitriles.[15] We have also used water to promote Ugi reactions,[7] but here this strategy did not provide a benefit.

In further developing this synthetic plan, we realized a better way to obtain 1-isocyanocyclohexene. Several previous preparations of this compound are known.[16] Armstrong prepared it by dehydration of *N*-cyclohex-1-enylformamide, but his synthesis

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(12) Tsang, J. W.; Schmied, B.; Nyfeler, R.; Goodman, M. *J. Med. Chem.* **1984**, *27*, 1663.
(13) (a) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842. (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574. (c) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631–4. (d) Gilley, C. B.; Kobayashi, Y. *J. Org. Chem.* **2008**, *73*, 4198–4204. (e) Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, *55*, 7411–7420. (f) Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999**, *64*, 336–337. (g) Kennedy, A. L.; Fryer, A. M.; Josey, J. A. *Org. Lett.* **2002**, *4*, 1167–70. (h) Rikimaru, K.; Yanagisawa, A.; Kan, T.; Fukuyama, T. A. *Synlett* **2004**, 41–43.
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SCHEME 2

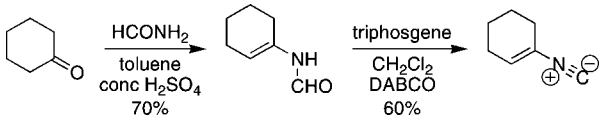
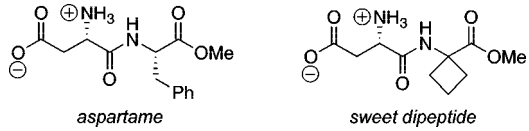


CHART 2

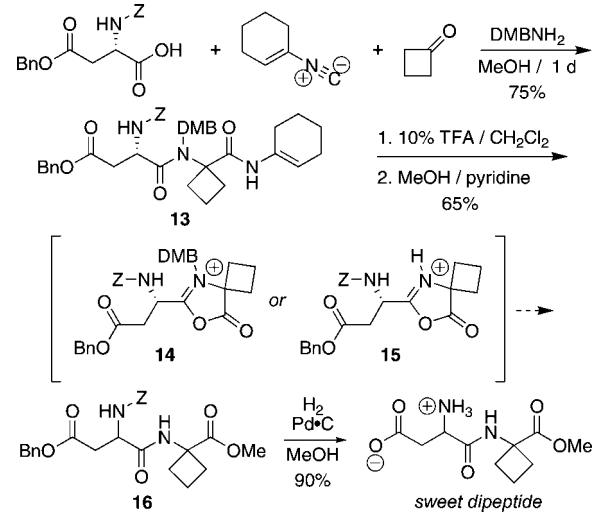


of that compound is not the most efficient. The best method to synthesize *N*-cyclohex-1-enylformamide is by acid-catalyzed condensation of formamide and cyclohexanone, very inexpensive starting materials,[17] whereas in our hands Armstrong's method proved best for the dehydration. 1-Isocyanocyclohexene was thereby conveniently synthesized in two steps in moderate yield by combining two known procedures that had not heretofore been used together.

The Ugi reaction uses 2,4-dimethoxybenzylamine as an easily deprotectable ammonia equivalent. The other reactants are cyclobutanone, Cbz-protected aspartic acid benzyl ester, and 1-isocyanocyclohexene. The Ugi reaction was performed in methanol, and the desired product **13** is obtained in good yield. In a previous incarnation of this synthesis, an Fmoc-protected aspartic acid was used.[18] Though this route failed owing to selectivity issues in deprotection steps, it taught a novel method to manipulate Ugi products similar to **13**. We initially converted the cyclohexenamide to the methyl ester (HCl/MeOH) and then removed the DMB group, done as usual with TFA.[19] To telescope two steps into one, we treated the Ugi product with TFA directly. Not only was the DMB group removed, but the amide was also hydrolyzed and the carboxylic acid was obtained upon quenching the reaction with water. When the reaction was quenched with methanol instead, the methyl ester was obtained, but in low yield. The addition of pyridine as a non-nucleophilic base to neutralize the excess TFA in the system increased the yield of methyl ester greatly. When this procedure was applied to **13**, the desired product **16** is obtained in acceptable yield, but the product proved to be racemic. We understand this reaction pathway as follows. Armstrong has shown that the utility of Ugi products of 1-isocyanocyclohexene derives from their ability to cyclize to oxazolones, which are fairly reactive acylating agents, inter alia. In the case at hand, such intermediates would correspond to **14** or **15** (depending on whether the DMB group was removed before or after the formation of the oxazolone). These intermediates presumably labilize the adjacent hydrogen for deprotonation, and when they are quenched with water, the carboxylic acid is formed, whereas if they are quenched with alcohol, the ester is formed.

Hydrogenolysis to remove the Cbz and benzyl groups proceeds in excellent yield following Goodman's procedure, completing the synthesis. The spectroscopic and physical properties match those reported by Goodman, establishing a brief route to cyclobutane dipeptide amides.

SCHEME 3



Discussion

One interesting aspect of an Ugi reaction of cyclobutanone (eq 1) is that it is accelerated when performed in water. We have previously suggested that the log *P* of reactants may indicate whether a particular reaction will be accelerated in water.[10] Polar, water-miscible compounds may not experience the hydrophobic effect that plays a role in the rate acceleration. The log *P* of cyclobutanone itself is only 0.59, likely too low to benefit from the aqueous reaction medium because it is water-miscible. However, we have previously shown that Ugi reactions with compounds even as polar as amino acids can benefit from being performed in water. We account for this observation based on the initial formation of an imine intermediate that is significantly more hydrophobic. The same consideration applies to the condensation of cyclobutanone with benzylamine, giving an imine with a log *P* of 2.78.

Passerini reactions of tetramethylcyclobutane-1,3-dione, *tert*-butyl isocyanide, and hydrophobic carboxylic acids are accelerated in water compared to methanol. However, the side product **7** is formed in some reactions. We envisioned that we might be able to "drive" the acid to react with the nitrilium ion by using more hydrophobic acids in the reactions in water. However, the data in Table 1 do not support a simple picture in which acid hydrophobicity determines the partitioning between Passerini products and **7**. The proportion of the Passerini product could be increased slightly by the addition of a larger excess of acid, but this ploy still does not surmount hydrolysis. That increasing the rate of nucleophilic addition of the acid to nitrilium ion **11** does *not* favor the formation of the Passerini product at the expense of the α-hydroxyamide suggests that water does not compete with the acid at this step to cause formation of **7**. That leaves the internal acyl-transfer reaction in **12** as the step where hydrolysis competes with formation of the desired product. The formation of **7** was suppressed by using a less sterically hindered (but also more hydrophobic) carboxylic acid, (adamantyl)acetic acid. Its hydrophobicity is comparable to adamantanecarboxylic acid, whose acyl-transfer reaction may be less facile because of the quaternary center flanking the carbonyl group. Similar hydrophobicity is exhibited by cyclohexanecarboxylic acid, which also gives a high yield. Pivalic acid and adamantanecarboxylic acid are more hydrophobic so as to encourage the addition step but too sterically hindered for a facile acyl transfer reaction to give the Passerini product, so

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the imidic anhydride in these cases is vulnerable to hydrolysis before it can rearrange.

It is surprising that Passerini reactions on tetramethylcyclobutane-1,3-dione proved possible. There are *no* other examples of Passerini reactions with ketones that are quaternary at both α carbons. The success of these reactions can be attributed to several factors, including the especially low LUMO energy of tetramethylcyclobutane-1,3-dione, which is even 0.83 eV lower than cyclobutanone.[4] Other factors favoring this process include the use of water as the solvent and the near-ideal ketone hydrophobicity (log P = 1.69) to exploit the hydrophobic effect in rate acceleration. It is also interesting that double-addition products are never observed despite using an excess of acid and isonitrile. This presumably reflects significant resistance of the initial Passerini product to addition to the remaining carbonyl, which must be sterically hindered by the other three quaternary ring carbons.

In summary, cyclobutanones have proved viable reaction partners in multicomponent reactions of isonitriles. The dipeptide synthesis also provided a new protocol for converting the products of Ugi reactions with 1-isocyanocyclohexene to other acyl derivatives with the simultaneous removal of an *N*-protecting group.

Experimental Section

1-(Benzylpropionylamino)cyclobutanecarboxylic Acid *tert*-Butylamide (3). Cyclobutanone (7.4 μL, 0.10 mmol), benzylamine (11 μL, 0.10 mmol), *tert*-butyl isocyanide (11 μL, 0.10 mmol), and propionic acid (7.5 μL, 0.10 mmol) were added into a glass vial (15 × 45 mm). Solvent (MeOH or H_2O) (1 mL) was then added. The reaction mixture was mixed by magnetic stirring or shaking at room temperature overnight. Workup procedures: For reaction in MeOH: The reaction mixture was concentrated, and the product was purified by flash chromatography (ethyl acetate/hexanes 1:5) to give **3** as a white solid (27 mg, 85%). For reaction in H_2O: The reaction mixture was extracted with CH_2Cl_2 (1 mL × 2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the product was purified by flash chromatography (ethyl acetate/hexanes 1:5) to give **3** as a white solid (25 mg, 80%). R_f = 0.19 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 7.20−7.39 (m, 5H), 4.45 (s, 2H), 2.68 (m, 2H), 2.15−2.40 (m, 4H), 1.70 (m, 2H), 1.34 (s, 9H), 1.06 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 175.9, 172.4, 138.1, 128.9, 127.2, 125.7, 66.6, 50.7, 49.1, 31.5, 28.7, 27.6, 14.6, 9.4. IR (neat): 3317, 2966, 2871, 1666, 1631, 1532, 1450, 1423, 1363, 1257, 1230, 1208, 1171, 1076, 1029, 972, 836, 815, 721, 695 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{29}N_2O_2$ [M + H]$^+$ 317.2229, found 317.2217. Mp: 91 °C (obtained with a Büchi B-545 instrument using the melting point method).

Cyclohexanecarboxylic Acid 1-*tert*-Butylcarbamoyl-2,2,4,4-tetramethyl-3-oxocyclobutyl Ester (5). Tetramethyl-1,3-cyclobutanedione (14 mg, 0.10 mmol), *tert*-butyl isocyanide (23 μL, 0.20 mmol), and cyclohexanecarboxylic acid (26 mg, 0.20 mmol) were added into a glass vial (15 × 45 mm). H_2O (1 mL) was then added. The reaction mixture was mixed by shaking at room temperature for 3 d and extracted with CH_2Cl_2 (1 mL × 2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the product was purified by flash chromatography (ethyl acetate/hexanes 1:5) to give **5** as a white solid (30 mg, 85%). R_f = 0.44 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 5.41 (s, 1H), 2.36 (tt, J = 11.1, 3.6 Hz, 1H), 1.94−2.39 (m, 2H), 1.79−1.87 (m, 2H), 1.45−1.77 (m, 4H), 1.41 (s, 6H), 1.35−1.39 (m, 1H), 1.32 (s, 9H), 1.29 (s, 6H), 1.19−1.26 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 217.3, 174.9, 167.7, 82.5, 64.0, 51.4, 43.4, 29.2, 28.7, 25.5, 25.3, 21.4, 19.8. IR (neat): 3410, 2932, 2854, 1774, 1740, 1684, 1513, 1452, 1368, 1314, 1288, 1247, 1218, 1155, 1125, 1066, 1030, 895, 830, 758 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{34}NO_4$ [M + H]$^+$ 352.2487, found 352.2488. Mp: 83 °C.

3-Methyl-but-2-enoic Acid 1-*tert*-Butylcarbamoyl-2,2,4,4-tetramethyl-3-oxocyclobutyl Ester (6). Tetramethyl-1,3-cyclobutanedione (14 mg, 0.10 mmol), *tert*-butyl isocyanide (23 μL, 0.20 mmol), and 3,3-dimethylacrylic acid (20 mg, 0.20 mmol) were added to a glass vial (15 × 45 mm). H_2O (1 mL) was then added. The reaction mixture was mixed by shaking at room temperature for 3 d and was extracted with CH_2Cl_2 (1 mL × 2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the product was purified by flash chromatography (ethyl acetate/hexanes 1:5) to give **6** as a white solid (10 mg, 31%) and **7** as a white solid (12 mg, 50%). **6**: R_f = 0.36 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 5.83 (m, 1H), 5.48 (s, 1H), 2.21 (d, J = 1.2 Hz, 3H), 1.98 (d, J = 1.2 Hz, 3H), 1.43 (s, 6H), 1.31 (s, 9H), 1.29 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 217.7, 168.1, 165.4, 160.5, 114.3, 82.3, 63.9, 51.3, 28.7, 27.5, 21.3, 20.4, 19.8. IR (neat): 3407, 2974, 2922, 1784, 1721, 1668, 1646, 1514, 1453, 1380, 1364, 1287, 1219, 1135, 1067, 1036, 931, 843, 827, 763, 734 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{30}NO_4$ [M + H]$^+$ 324.2174, found 324.2176. Mp: 88 °C. **7**: R_f = 0.49 (ethyl acetate/hexanes 1:2). ^{1}H NMR ($CDCl_3$): δ 6.78 (s, 1H), 2.57 (s, 1H), 1.37 (s, 9H), 1.32 (s, 6H), 1.31 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 217.6, 169.8, 78.3, 63.5, 51.1, 28.8, 20.8, 20.1. IR (neat): 3403, 3364, 2971, 2925, 1773, 1651, 1525, 1457, 1364, 1328, 1249, 1227, 1203, 1167, 1122, 1055, 1024, 991, 979, 909, 831, 761, 725, 664 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{24}NO_3$ [M+H]$^+$ 242.1756, found 242.1761. Mp: 146 °C.

2,2-Dimethylpropionic Acid 1-*tert*-Butylcarbamoyl-2,2,4,4-tetramethyl-3-oxocyclobutyl Ester (8). This compound was synthesized as above using trimethylacetic acid. The product was obtained as a white solid (7.0 mg, 20%). Side product **7** was afforded as a white solid (10 mg, 39%). **8**: R_f = 0.40 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 5.32 (s, 1H), 1.35 (s, 6H), 1.25 (s, 9H), 1.25 (s, 9H), 1.23 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 217.3, 177.2, 167.8, 82.6, 64.2, 51.6, 39.4, 28.8, 27.3, 21.5, 19.9. IR (neat): 3418, 2972, 2932, 1770, 1745, 1721, 1680, 1519, 1451, 1379, 1365, 1281, 1231, 1220, 1187, 1125, 1072, 1030, 963, 877, 849, 830, 794, 771, 727 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{32}NO_4$ [M + H]$^+$ 326.2331, found 326.2320. Mp: 99 °C.

Adamantane-1-carboxylic Acid 1-*tert*-Butylcarbamoyl-2,2,4,4-tetramethyl-3-oxocyclobutyl Ester (9). Compound **9** was synthesized as a colorless oil (24 mg, 60%) as in example **6** starting with 1-adamantanecarboxylic acid. R_f = 0.49 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 5.38 (s, 1H), 2.07 (brs, 3H), 1.96 (m, 6H), 1.75 (m, 6H), 1.40 (s, 6H), 1.31 (s, 9H), 1.28 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 217.4, 176.3, 167.7, 82.2, 64.0, 51.4, 41.2, 39.1, 36.3, 28.8, 27.8, 21.5, 19.7. IR (neat): 3448, 2969, 2907, 2853, 1781, 1738, 1684, 1506, 1453, 1365, 1216, 1182, 1103, 1067, 1032, 978, 889, 744, 686 cm^{-1}. HRMS (ESI): calcd for $C_{24}H_{38}NO_4$ [M + H]$^+$ 404.2800, found 404.2806. Side product **7** was afforded as a white solid (3.0 mg, 12%).

Adamantan-1-ylacetic Acid 1-*tert*-Butylcarbamoyl-2,2,4,4-tetramethyl-3-oxocyclobutyl Ester (10). Compound **10** was synthesized as a colorless oil (41 mg, 98%) as in example **6** starting with 1-adamantaneacetic acid. R_f = 0.45 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 5.47 (s, 1H), 2.23 (s, 2H), 2.01 (m, 3H), 1.61−1.78 (m, 12H), 1.42 (s, 6H), 1.34 (s, 9H), 1.29 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 217.3, 171.0, 167.9, 83.0, 64.0, 51.6, 48.0, 42.3, 36.6, 32.9, 28.8, 28.4, 21.5, 19.9. IR (neat): 3447, 3401, 2903, 2849, 1780, 1744, 1683, 1505, 1453, 1366, 1284, 1218, 1190, 1125, 1064, 1032, 980, 888, 829, 731 cm^{-1}. HRMS (ESI): calcd for $C_{25}H_{40}NO_4$ [M + H]$^+$ 418.2957, found 418.2946.

3-Benzyloxycarbonylamino-*N*-[1-(cyclohex-1-enylcarbamoyl)-cyclobutyl]-*N*-(2,4-dimethoxybenzyl)succinamic Acid Benzyl Ester (13). *Z*-β-(Benzyl ester)-L-aspartic acid (36 mg, 0.10 mmol), 2,4-dimethoxybenzylamine (15 μL, 0.10 mmol), cyclobutanone (8.0 μL, 0.10 mmol), and 1-isocyanocyclohexene (0.10 mL of a 1 M

solution in pentane, 0.10 mmol) were dissolved in 1 mL of MeOH in a 10 mL round-bottom flask with a stir bar. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo. The product was purified by flash chromatography (ethyl acetate/hexanes 1:2) to afford **13** as a white solid (51 mg, 75%). $R_f = 0.37$ (ethyl acetate/hexanes 1:2). ^{1}HNMR ($CDCl_3$): δ 8.10 (s, 1H), 7.34 (m, 10H), 7.00 (d, $J = 8.4$ Hz, 1H), 7.39 (dd, $J = 8.7$, 1.8 Hz, 1H), 6.32 (d, $J = 1.8$ Hz, 1H), 5.11−5.75 (m, 2H), 5.11 (s, 2H), 5.07 (s, 2H), 4.53 (d, $J = 15.9$ Hz, 1H), 4.34 (d, $J = 16.5$ Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 2.54−2.86 (m, 4H), 1.95−2.24 (m, 4H), 1.50−1.65 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 172.3, 170.7, 170.5, 161.1, 158.4, 155.5, 136.4, 135.6, 133.0, 130.0, 128.8, 128.7, 128.5, 128.5, 128.4, 128.2, 116.1, 111.7, 104.0, 98.6, 67.2, 67.0, 66.4, 55.5, 55.1, 49.4, 45.3, 38.1, 32.0, 30.8, 27.9, 24.1, 22.8, 22.3, 14.9. IR (neat): 3300, 2938, 2837, 1723, 1683, 1614, 1589, 1507, 1455, 1438, 1383, 1287, 1259, 1208, 1158, 1029 cm^{-1}. HRMS (ESI): calcd for $C_{39}H_{46}N_3O_8$ $[M + H]^+$ 684.3285, found 684.3318. Mp: 51 °C. $[\alpha]^{25}_D$ − 20.66 (*c* 0.75, MeOH).

1-(3-Benzyloxycarbonyl-2-benzyloxycarbonylaminopropionylamino)cyclobutanecarboxylic Acid Methyl Ester (16). TFA (0.80 mL) was added to a solution of compound **13** (55 mg, 80 μmol) in methylene chloride (5 mL) in a 25 mL round-bottom flask. The resulting mixture (purple solution) was stirred at room temperature for 1 h. MeOH (4.0 mL) and anhydrous pyridine (0.90 mL) were added to the reaction mixture. The solution turned cloudy yellow. The reaction mixture was stirred at room temperature for 1 h and concentrated in vacuo. Methylene chloride (20 mL) was added to dissolve the residue. The organic solution was washed with water (2 × 10 mL), dried over Na_2SO_4, and then concentrated in vacuo. The product was purified by flash chromatography (ethyl acetate/hexanes 1:2) to afford **16** as a colorless oil (24 mg, 65%). This is a known compound.[12] $R_f = 0.22$ (ethyl acetate/hexanes 1:2). ^{1}H NMR ($CDCl_3$): δ 7.31−7.37 (m, 10H), 7.04 (s, 1H), 5.92 (m, 1H), 5.13 (m, 4H), 4.61 (m, 1H), 3.70 (s, 3H), 3.06 (dd, $J = 17.1$, 4.2 Hz, 1H), 2.73 (dd, $J = 16.8$, 6.3 Hz, 1H), 2.55−2.66 (m, 2H), 2.27 (m, 2H), 1.90−2.10 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 173.6, 171.8, 170.2, 156.2, 136.2, 135.5, 128.8, 128.8, 128.6, 128.5, 128.5, 128.3, 67.5, 67.1, 58.6, 52.7, 51.0, 36.4, 31.5, 31.5, 15.5. IR (neat): 3320, 2953, 1728, 1667, 1498, 1455, 1386, 1312, 1214, 1168, 1123, 1047, 1028, 984, 911, 844, 737, 696 cm^{-1}. HRMS (ESI): calcd for $C_{25}H_{29}N_2O_7$ $[M + H]^+$ 469.1969, found 469.1961.

Aspartyl-α-aminocyclobutanecarboxylic Acid Methyl Ester. Compound **16** (23 mg, 50 μmol) was dissolved in MeOH (1 mL). Nitrogen was bubbled into the solution for 10 min. Palladium black (10 wt % on carbon powder, 10 mg) was added at once. Nitrogen was bubbled through for an additional 5 min, and hydrogen was bubbled through the solution for 4 h. After filtration, the solvent was removed in vacuo. The product was purified by recrystallization from MeOH/ether to afford the title compound as a white solid (11 mg, 90%). ^{1}H NMR (acetone-d_6): δ 4.05 (dd, $J = 8.7$, 3.9 Hz, 1H), 3.71 (s, 3H), 2.49−2.78 (m, 4H), 2.15−2.34 (m, 2H), 1.98−2.10 (m, 2H). ^{13}C NMR (acetone-d_6): δ 176.3, 175.0, 170.1, 59.8, 53.1, 52.3, 38.4, 32.4, 32.3, 16.6. IR (neat): 3257, 2951, 1743, 1663, 1558, 1379, 1323, 1260, 1203, 1164, 1121, 1068, 993, 921, 802, 773 cm^{-1}. HRMS (ESI): calcd for $C_{10}H_{17}N_2O_5$ $[M + H]^+$ 245.1137, found 245.1136. Mp: 115 °C dec (lit.[12] mp 112−113 °C dec). This is a known compound, and these properties were identical to those published.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for **3**, **5**−**10**, **13**, **16**, and aspartyl-α-amino-cyclobutanecarboxylic acid methyl ester. This material is available free of charge via the Internet at http://pubs.acs.org.

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