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Boc-protected 1-(3-oxocycloalkyl)ureas via a one-step Curtius rearrangement: mechanism and scope

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Carbamoylcarbamate

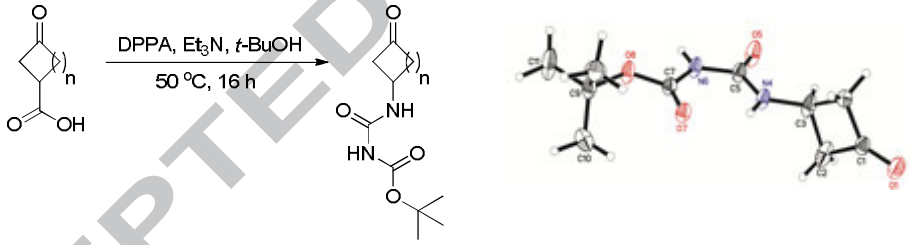
γ-Keto carboxylic acid

1-(3-Oxocyclobutyl) carboxylic acid

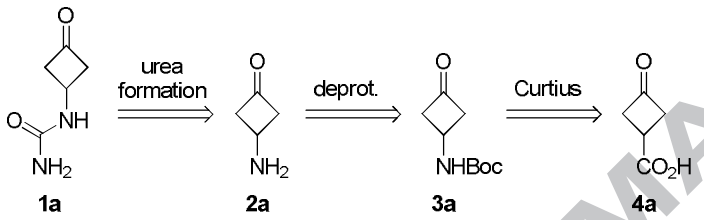
Abstract

1-(3-Oxocyclobutyl) carboxylic acid (**4a**) was converted into *N*-Boc-protected 1-(3-oxocyclobutyl) urea (**5a**), a key intermediates for the preparation of agonists of metabotropic glutamate receptor 5, in one-step when treated with diphenyl phosphoryl azide and triethylamine in *tert*-butanol. The mechanism of the reaction involves a nucleophilic addition of the *in situ* generated *tert*-butyl carbamate to the isocyanate intermediate. This reaction is applicable to other 1-(3-oxocycloalkyl) carboxylic acids but not to linear γ-keto carboxylic acids.

Graphic Abstract



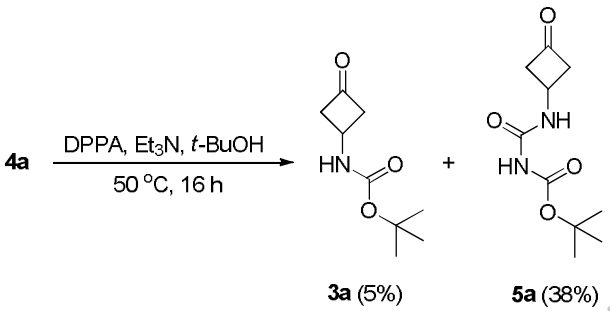
In the course of our research in developing novel agonists for metabotropic glutamate receptor subtype 5 (mGluR5), we were interested in the synthesis of 1-(3-oxocyclobutyl)urea (**1a**), a key intermediate to various small molecule agonists of mGluR5. To synthesize **1a**, we planned to form the urea beginning with 3-aminocyclobutanone (**2a**, Scheme 1).[1] Although several synthetic routes are known for the generation of **2a**, they usually require multiple steps and/or often give poor overall yields.[2] To obtain amine **2a** rapidly and efficiently, we attempted to use the Curtius rearrangement to directly convert carboxylic acid **4a** into carbamate **3a**,[3] which in turn, can easily lead to **2a** after removing the *N*-protecting group.



Scheme 1. Synthetic plan to **1a**.

Our initial effort was to synthesize *tert*-butyl 3-oxocyclobutylcarbamate (**3a**). To generate **3a**, a solution of **4a** in *tert*-butanol (*t*-BuOH) was treated with diphenyl phosphoryl azide (DPPA)[4] and triethylamine (Et_3N). After heating the reaction mixture at 50 ºC for 16 h, a major product was isolated in 38% yield. To our surprise, mass spectrum and ^1H NMR data of the product did not match those of the anticipated product (**3a**). This major product only has an ($M+H^+$) peak at 229, which was 43 daltons more than the calculated molecular weight of **3a** ($M+H^+$ = 186), implying a possible insertion of a –CONH– fragment into the desired product. This speculation was confirmed by the fact that there was an extra singlet at 8.10 ppm (integrating to one proton) in the ^1H NMR spectrum of the product in $CDCl_3$. Further ^{13}C NMR data showed a peak at 204.7 ppm, indicating the retaining of the ketone functionality. More interestingly, after treating this compound with trifluoroacetic acid (TFA), urea **1a** was isolated and characterized. On the basis of these results, we assigned the product of the original reaction as *tert*-butyl *N*-((3-oxocyclobutyl) carbamoyl)carbamate (**5a**, Scheme 2). The chemical structure of **5a** was confirmed

by single crystal X-ray analysis (Figure 1 and Table 1). The crystallographic analysis showed that the N4 participated in intramolecular hydrogen bonding with the carbonyl group, the N4–H···O7 hydrogen bond length was 2.08 Å (Table S7), which explained the downfield shift of the corresponding signal (8.10 ppm) in the ^{1}H NMR. In addition to **5a**, the desired product (**3a**) was isolated as a relatively non-polar compound with only 5% yields. It is also noted that upon heating at 85 °C for 2 h, the cyclobutanone ring of **3a** broke to form a significant amount of the α,β-unsaturated methylketone. The thermal instability of **3a** might also account for the low yield of previously reported methods to this compound.[2c]



Scheme 2. The Curtius rearrangement of **4a** in *t*-BuOH.

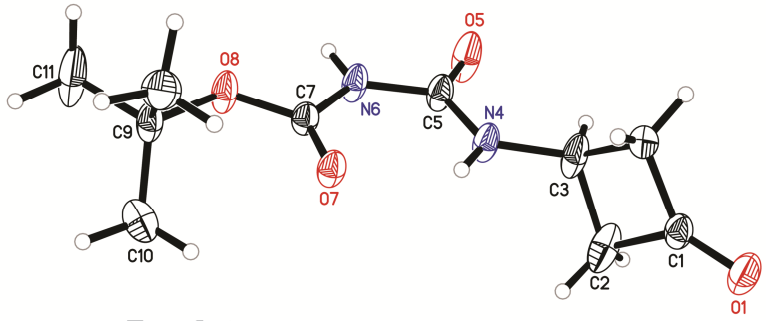


Figure 1. Single crystal structure of compound **5a**.

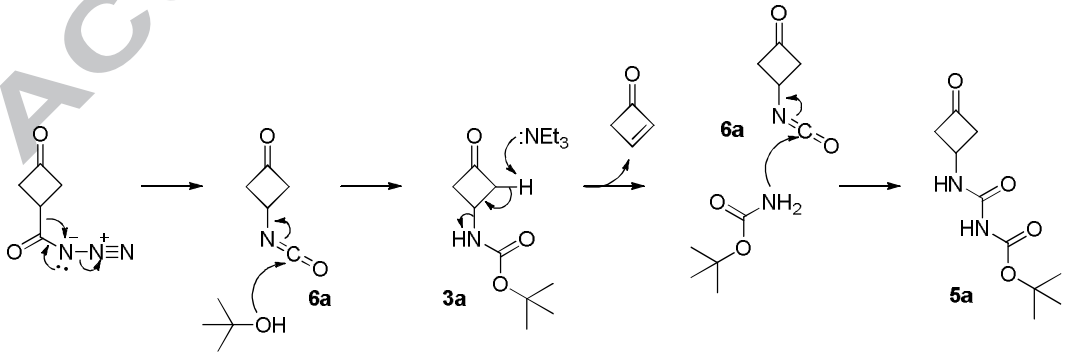
Table 1

Selected crystallographic data of **5a**

Empirical formula	$C_{10}H_{16}N_2O_4$
Formula weight	228.25
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P n m a
Unit cell dimensions	a = 24.798(2) Å, □= 90°

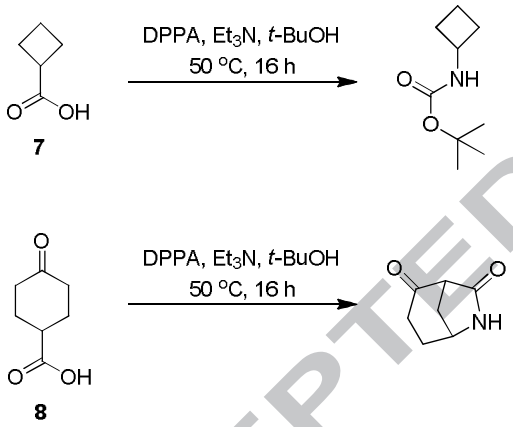
	b = 9.0377(7) Å, □= 90° c = 5.2093(4) Å, □ = 90°
Volume	1167.49(16) Å^3
Z	4
Density (calculated)	1.299 Mg/m^3
Absorption coefficient	0.101 mm^{-1}
F(000)	488
Crystal size	0.617 × 0.431 × 0.157 mm^3

To elucidate the origin of **5a**, the reaction was repeated in which carboxylic acid **4a** was treated with DPPA and Et_3N in *t*-BuOH and monitored closely by thin layer chromatography (TLC). Time course studies clearly showed the disappearance of the starting material (**4a**) and the emergence of carbamate **3a** within the first hour of the reaction. However, the amount of **3a** generated did not change significantly during the course of reaction. After stirring the reaction for 2 h, compound **5a**, with significantly higher polarity to that of **3a**, was formed and built up. Accordingly, we speculated that **3a** might be an intermediate, which was transformed into **5a** by the insertion of the –CONH– fragment. Specifically, we proposed that at the beginning of the reaction, Curtius rearrangement of **4a** formed isocyanate **6a**, which was then attacked by *t*-BuOH to generate carbamate **3a** (Scheme 3). Since compound **3a** was not stable under basic environment, it lost a molecule of *tert*-butyl carbamate via elimination to form cyclobut-2-enone.[5] The resulting *tert*-butyl carbamate attacked the isocyanate group of **6a** in the reaction mixture to generate compound **5a**. It is noted that the theoretical yield of the reaction is 50%, which explains the relatively modest yields of compound **5a**.



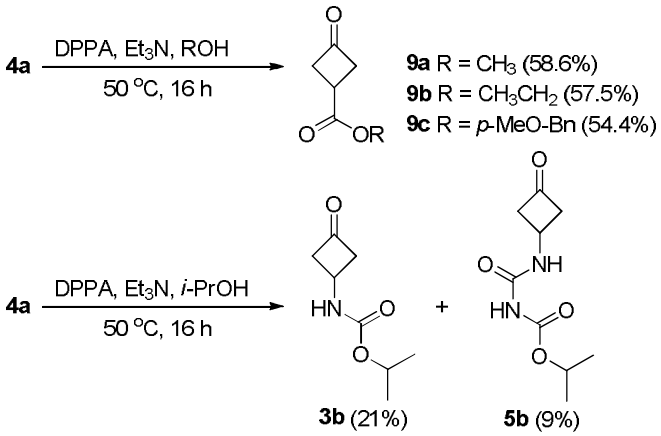
Scheme 3. Proposed reaction mechanism for the formation of **5a** in *t*-BuOH.

To test this hypothesis, we carried out reactions under the same conditions starting with cyclobutanecarboxylic acid (**7**) and 4-oxocyclohexanecarboxylic acid (**8**). For both reactions, no carbamoylcarbamates were detected (Scheme 4). When **7** was used, the normal Curtius product *tert*-butyl cyclobutylcarbamate was isolated in good yields. This result indicated that without the presence of the γ-carbonyl group, the Curtius product was stable and no elimination of *tert*-butyl carbamate happened. On the other hand, treatment of **8** with the same conditions generated bicyclic 6-azabicyclo[3.2.1]octane-2,7-dione.[6] These results confirmed that the presence of the γ-keto acid group to the carboxylic acid functionality was essential for the generation of carbamoylcarbamates, which accelerated the elimination of *tert*-butyl carbamate from carbamate **3a**.



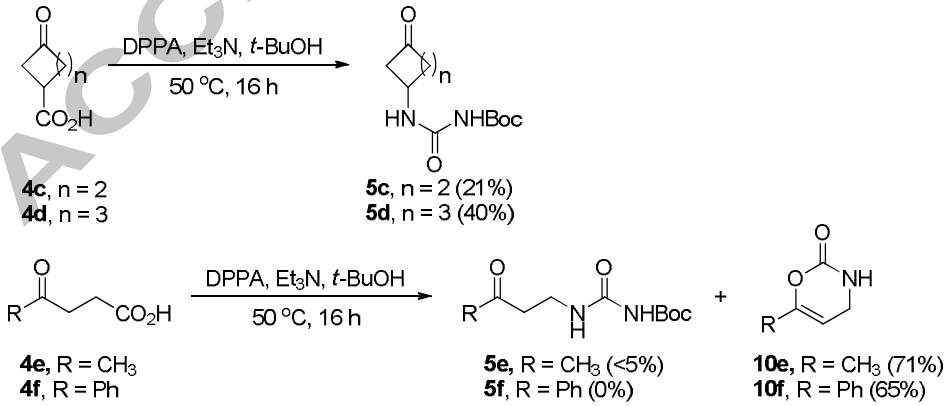
Scheme 4. Reactions starting with compounds **7** and **8**.

We also repeated the reaction of **4a** with DPPA and Et_3N in other alcohols (Scheme 5). When sterically less hindered primary alcohols (e.g., MeOH, EtOH, and *p*-methoxybenzyl) were used, the corresponding esters were isolated as the only products (**9a-c**) in good yields. On the other hand, the reaction performed in *i*-PrOH gave carbamate **3b** as the major product. Although the *iso*-propyl *N*-((3-oxocyclobutyl)carbamoyl)carbamate (**5b**) was also isolated, the yield was significantly less than that of **5a** from the previous reaction in *t*-BuOH. These results indicated that the outcome of the reaction was largely controlled by the nucleophilicity of the alcohols involved in the reactions.



Scheme 5. The Curtius rearrangement of **4a** in other alcohols.

To study the scope of the reaction, similar reactions were conducted under similar conditions using other *γ*-keto acids (Scheme 6). When 3-oxocyclopentanecarboxylic acid (**4c**) and 3-oxocyclohexanecarboxylic acid (**4d**) were used, the corresponding Boc-protected 1-(3-oxo)ureas (**5c** and **5d**) were obtained as the major products. However, the reactions starting with non-cyclic *γ*–keto acids **4e** and **4f** generated compounds **5e** and **5f** in minimum yields, instead, 3,4-dihydro-2*H*-1,3-oxazin-2-ones **10e** and **10f** were isolated as the major products. The chemical structure of compound **10e** was confirmed by single crystal X-ray analysis (Figure 2). These results showed that the formation of carbamoyl carbamates was only applicable to 1-(3-oxocycloalkyl)carboxylic acids, as for the starting materials employing a non-cyclic *γ*–keto carboxylic acid functionality, the reaction will favor the formation of 3,4-dihydro-2*H*-1,3-oxazin-2-ones via an intramolecular cyclization mechanism.



Scheme 6. Reaction results using *γ*–keto acids **4c-f.**

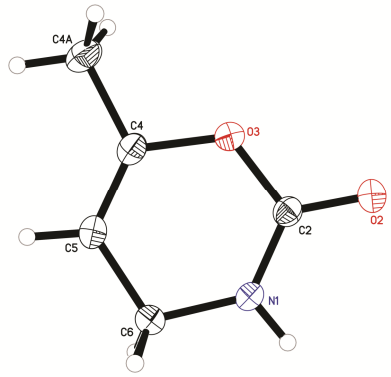


Figure 2. Single crystal structure of compound **10e**.

In summary, we report an unexpected one-step formation of Boc-protected 1-(3-oxo)ureas starting with 1-(3-oxo)acids. In the reaction mechanism, the initially generated carbamate product from the Curtius rearrangement was not stable. It eliminated the *tert*-butyl carbamate that attacks the isocyanate intermediate in the reaction mixture to generate the final product. The application of this method has been highlighted by a rapid preparation of urea **1a**, a key fragment for the development of agonists for mGluR5. The conditions described herein is applicable to the preparation of other 1-(3-oxocycloalkyl)ureas.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online.

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Graphic Abstract