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

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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.

Keywords

1-(3-Oxo)ureas; Curtius rearrangement; Carbamoylcarbamate; γ-Keto carboxylic acid; 1-(3-Oxocyclobutyl) carboxylic acid

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.

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

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 °C 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 ^1H 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]

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**.

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**.

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.

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-oxocyclo-hexanecarboxylic 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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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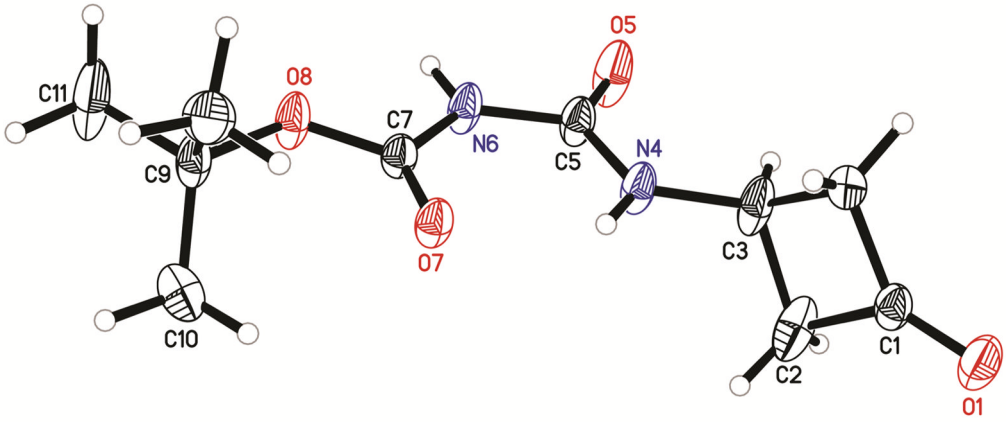


Figure 1.
Single crystal structure of compound **5a**.

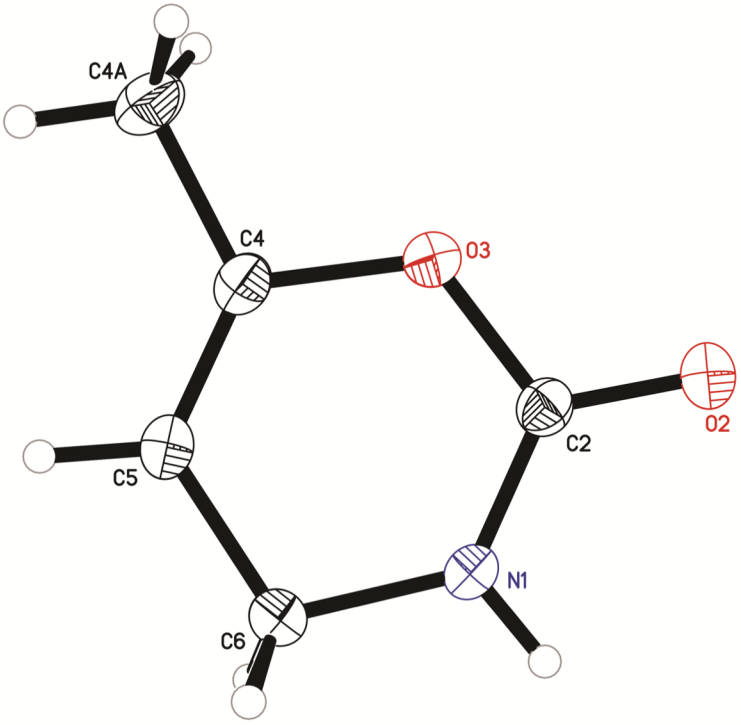
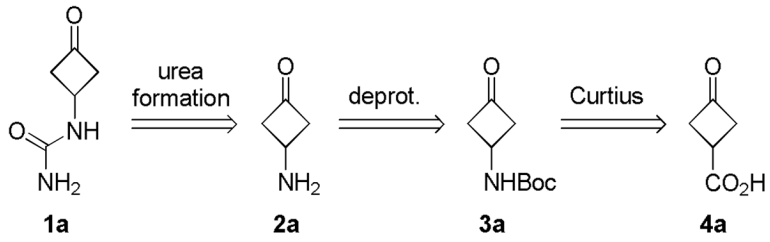
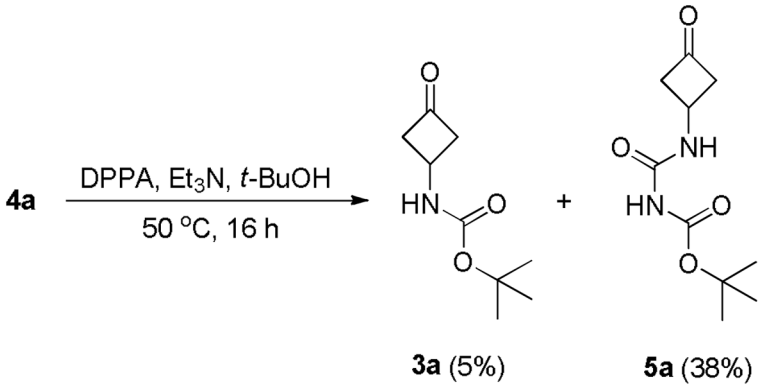


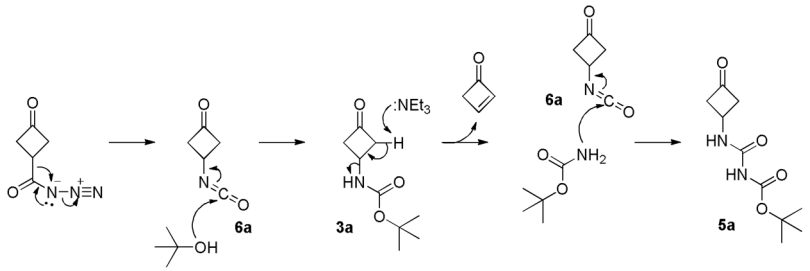
Figure 2.
Single crystal structure of compound **10e**.



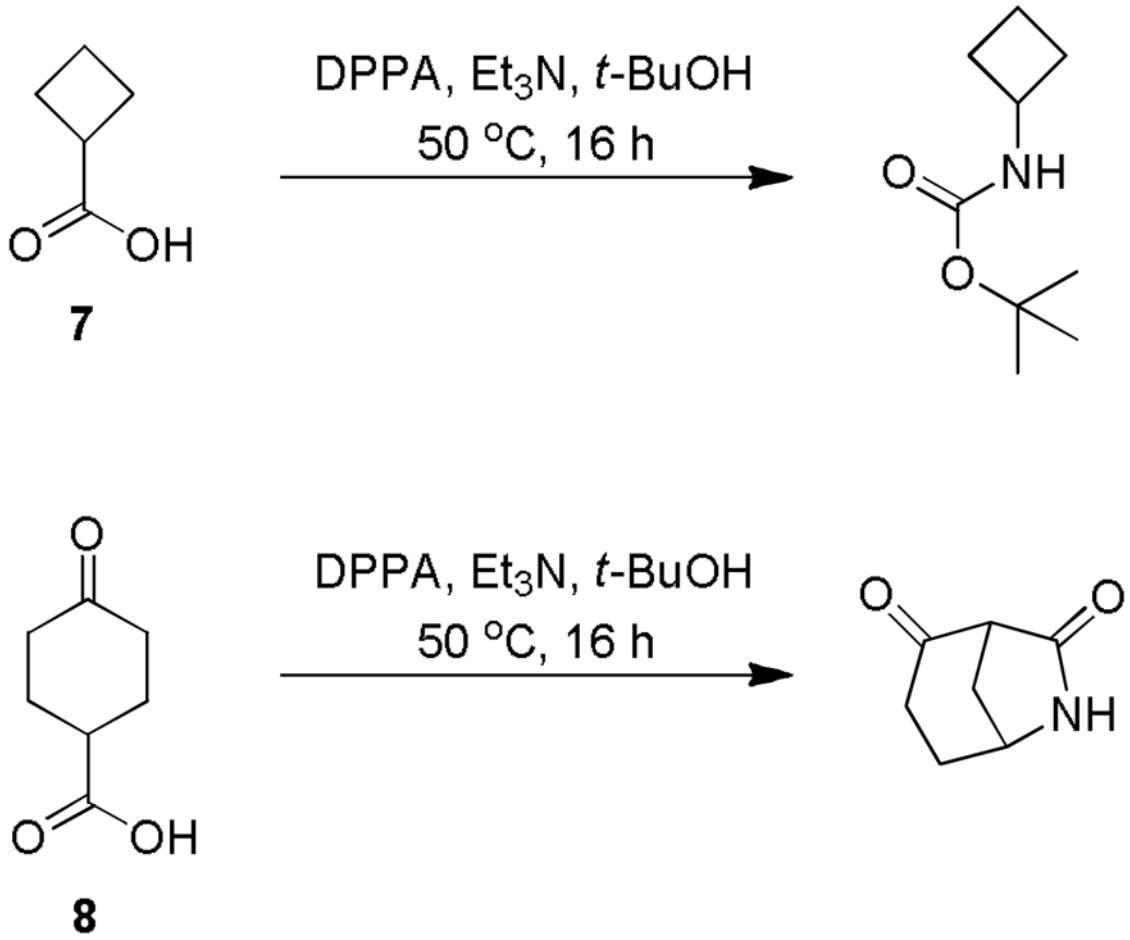
Scheme 1.
Synthetic plan to **1a**.



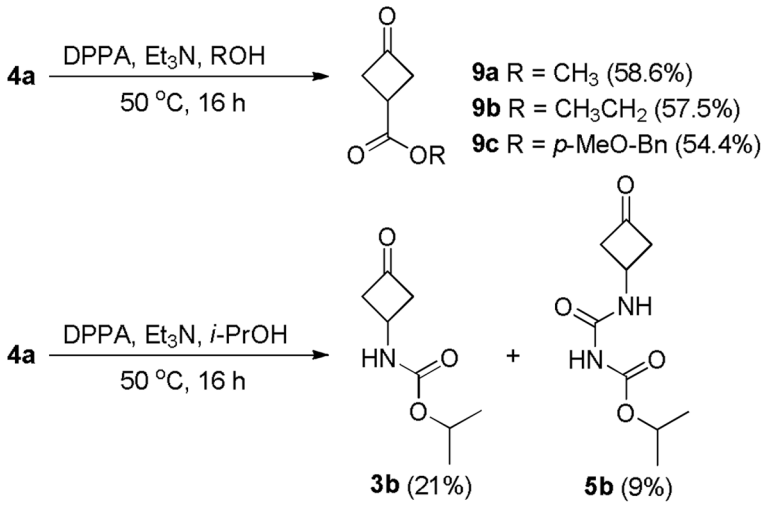
Scheme 2.
The Curtius rearrangement of **4a** in *t*-BuOH.



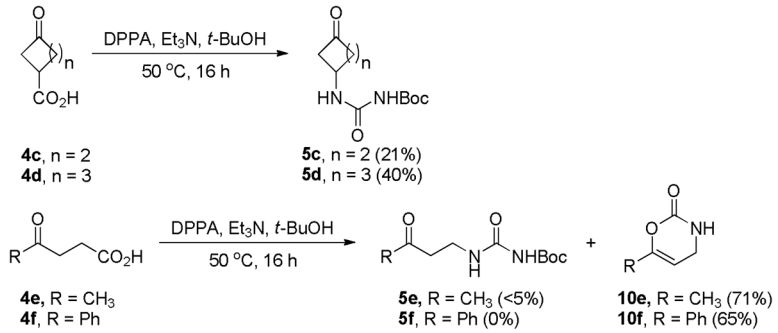
Scheme 3.
Proposed reaction mechanism for the formation of **5a** in *t*-BuOH.



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



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



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

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, Y= 90° b = 9.0377(7) Å, Y= 90° c = 5.2093(4) Å, Y= 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