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Activation of carboxylic acids by Burgess reagent: an efficient route to acyl ureas and amides

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Abstract—Carboxylic acids upon treatment with Burgess reagent are converted to novel mixed sulfocarboxy anhydrides. Subsequent treatment of such mixed anhydrides with amines at elevated temperatures yields acyl ureas and amides. The ratio of the two products appears to be temperature controlled. The method provides a simple and convenient route to diverse acyl ureas starting from carboxylic acids and amines.

Burgess reagent has been a versatile agent in organic synthesis for decades. Over the years it has been employed in diverse transformations such as dehydrations of alcohols to alkenes[1] and amides to nitriles[2] or synthesis of oxazolines[3] and thiazolines.[4] It has also been noted that primary alcohols can be converted to the corresponding methyl carbamates[5] and that the reaction of Burgess reagent with epoxides can lead to cyclic sulfamidates.[6] Sulfamidates have also been prepared from 1,2-diols or epoxyalcohols, while sulfamides are the products starting from aminoalcohols using the agent.[7] An immobilized version of the Burgess reagent has been found to work with similar outcome as the solution phase reagent in the synthesis of oxadiazoles.[8]

Surprisingly, no report has been published on reacting Burgess-type reagents with carboxylic acids. We speculated whether acids could be activated by the reagent to give a mixed anhydride derivative, which upon treatment with amines could lead to amides. Indeed, our tests indicated that an active species is formed almost instantaneously, however, treatment with amines at 150 °C yields predominantly acyl ureas while amide formation is favored at lower temperatures.

The acyl urea moiety has been an important functional group in medicinal chemistry and has been incorporated in marketed drugs as well as investigational candidates. The synthesis of acyl ureas has typically been achieved via condensation of either acylisocyanates with amines or isocyanates with amides.[9] Alternative routes starting from ureas such as boronic acid-catalyzed condensation with acids[10] or acylation using alkenyl esters[11] have also been disclosed. Our results represent the first synthesis of acyl ureas directly from carboxylic acids and amines.

The initial attempts to mix the Burgess reagent with acids were carried out in tetrahydrofuran but the reaction turned instantly heterogeneous. In addition, many acids had rather poor solubility. A more polar solvent, dimethylacetamide, was used successfully as an alternative. Unfortunately, the large solvent signal observed by LC–MS made the careful study of the various intermediate species difficult. Ultimately, we decided to run the reactions in acetonitrile for reasons as follows. In acetonitrile there is no solvent peak in the UV, ELSD, or mass spectrum, the solvent has a low boiling point and good microwave absorption, and it does not generate dimethylamine, a competing nucleophile during urea formation. Diisopropylethylamine (DIPEA) was employed as an additive to avoid solubility issues with the reactant acids. The Burgess reagent is quite stable but we noticed that, after prolonged exposure to ambient conditions, an increasing excess was required for complete acid consumption. The excess active reagent,

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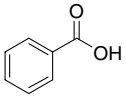
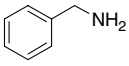
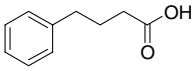
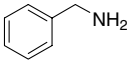
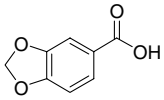
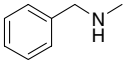
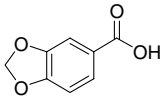
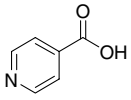
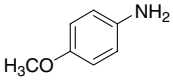
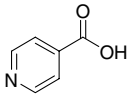
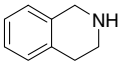
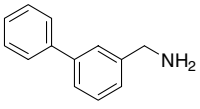
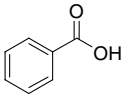
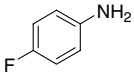
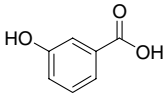
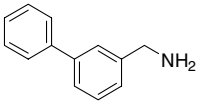
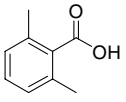
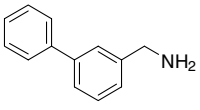
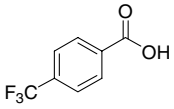
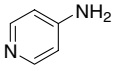
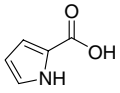
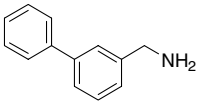
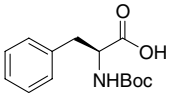
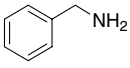
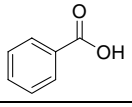
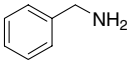
however, readily reacts with amines at room temperature to result in sulfamidates, which is in accord with recent reports.[7] As such, it was critical to destroy the excess reagent prior to amine addition. This was easily accomplished by heating the reaction mixture to 80 °C for 15 min. No sulfamidates could be detected once the amines were added *subsequent* to heating, while complex **2** appeared unscathed. The mass spectrum in the LCMS of novel intermediates **2** derived from all acids indicated a strong signal for the parent ion in negative

Table 1. Products (**5/4**) obtained via synthetic route (b) in Scheme 1

Entry	Acid	Amine	Method	Yield[a]
a			1	35/15
b			1	10/25
c			1	50/0
d			1	30/0
e			1	40/5
f			1	45/35
g			1	25/15
h[b]			1	50/0
i			1	45/15
j			1	5/20
k			1	40/5
l			1	0/0
m			1	15/25
n			2	50/10

[a] Isolated yields for acyl ureas/amides (%).
[b] Purified by filtration of crude mixtures due to poor solubility under HPLC conditions.

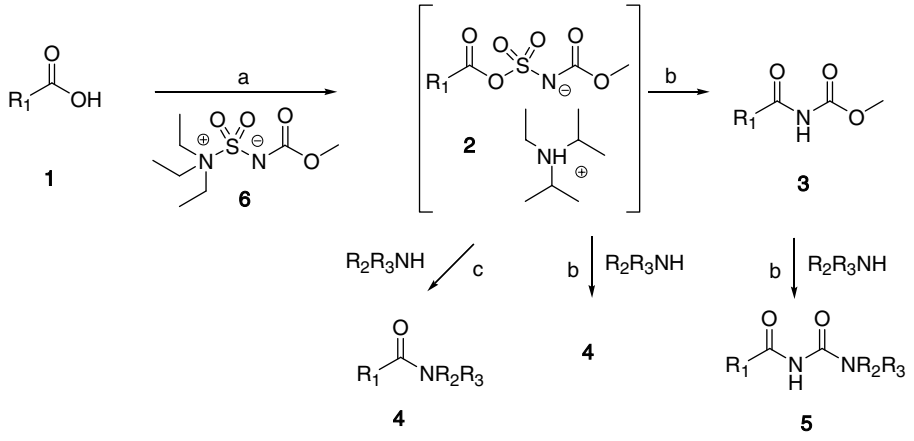
mode electrospray and a weaker di-sodiated *m*/*z* of the parent ion in positive mode electrospray. Intermediate **2a** (R_1 = phenyl, Table 1) was purified by HPLC and further characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. All data were consistent with the proposed structure **2** in Scheme 1. Frequently, we also observed another smaller UV and mass signal in the LCMS corresponding to the sodiated ion of the acyl urethanes **3**. The acyl urethanes of entries **2a**,**b** were also purified and the structures were confirmed by matching the ^{1}H NMR spectrum to that in the literature.

The ratio of the acyl urea and amide products in our experience is governed by the relative rates of conversion of intermediate **2** to either the corresponding amide **4** or urethane **3**. Amide formation for the more reactive alkyl carboxylic acids is much faster and cleaner than that for aryl acids. The same effect in route (b) in Scheme 1 results in a significant amount of amide by-product for alkyl acids as the temperature ramp-up time is sufficient to convert a large portion of **2** to the amides. To confirm this hypothesis, purified **3a** was heated under conditions identical to route (b). Clean conversion to acyl urea **5a** without any detectable amide formation was observed by LCMS. In addition, the rearrangement required for conversion of **2** to **3** was easily blocked by two *ortho* methyl groups in entry **5j** and thus only traces of the acyl urea could be isolated along with the amide product. This rearrangement is proposed to be analogous to the one required for the formation of methyl carbamates from primary alcohols.[5] Little amide formation is observed for unhindered aryl acids under the standard conditions toward acyl ureas. No amide could be detected, however with the hindered *tert*-butylamine (**5d**), which further substantiates the mechanism put forth herein. Amides cannot typically be synthesized in reactions of similar hindered nucleophiles and active esters such as *p*-nitrophenyl or pentafluorophenyl esters. It was also important to verify that the route to acyl ureas **5** does not go through amides **4** due to the amine reacting with a decomposition product of Burgess reagent. To that extent, we heated crude amide mixtures obtained at 80–150 °C but no acyl ureas were detected.

A limited set of experiments was done to optimize the experimental conditions for acyl urea formation. Longer reactions led to product degradation, higher and lower temperatures resulted in decreased purity. Conventional heating gave comparable ratios of amides and corresponding acyl ureas for aryl acids but higher amide ratios for alkyl acids (data not shown). In general microwave heating appeared to deliver somewhat higher yields. The acyl urea products of primary amines for most (especially aryl) entries precipitate in acetonitrile upon cooling. To achieve a generally applicable parallel process the solvent was stripped off and the residue was dissolved in DMSO for preparative HPLC purification. The ratio for the isolated products was verified by analysis of the LCMS UV spectra of the crude mixtures using the purified samples as controls for normalization. We made no attempt to further optimize the reaction conditions or workup procedures for the individual entries, although, some sensitive functional groups (such as hydroxyl, amino, or Boc) may clearly benefit from custom conditions.

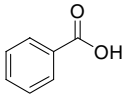
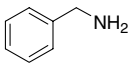
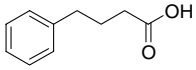
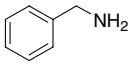
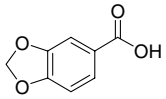
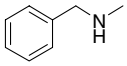
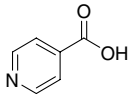
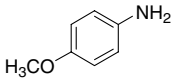
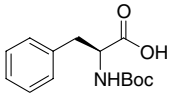
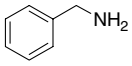
The method is rather insensitive to the electronic and steric nature of the nucleophile in preparation of the acyl ureas (Table 1). Both electron rich and electron deficient aryl amines and alkyl amines work equally well. In fact, less reactive amines lead to higher acyl urea ratios as route (c) toward amides is shut down. On the other hand, significant steric hindrance on the acid blocks the conversion of **2** to acyl urethanes as exemplified by entry **5j**. No significant conversion to amides takes place with amines of low nucleophilicity. Both primary and secondary amines react equally well and no significant electronic effect on the acid side was observed in either routes (b) and (c). The failure of pyrrole-2-carboxylic acid (**5l**) signals that the known high reactivity of the Burgess reagent with amines and alcohols does require these functional groups present in the carboxylic acid be protected. Boc protection was tolerated in the microwave under both routes (b) and (c) conditions.

Route (c) leads to no acyl urea products albeit amides for aryl acids were found to be contaminated by variable



Scheme 1. Reaction of carboxylic acids with Burgess reagent and amines. Reagents and conditions: (a) acetonitrile (1 mL/0.1 mmol acid), DIPEA (1.5 equiv), 5 min at rt; Burgess reagent (**6**, 1.4 equiv), 5 min at rt; 15 min at 80 °C (μw); (b) R_2R_3NH (1.5 equiv), 8 min at 150 °C (μw); (c) R_2R_3NH (3 equiv), 1 h at 80 °C (μw).

Table 2. Amides obtained via synthetic route (c) in Scheme 1

Entry	Acid	Amine	Yield[a]
4a			40
4b			65
4c			20
4e			0
4m			35

[a] Isolated yields for amides (%).

amounts of acyl urethanes **3**. While the isolated yields for amides were modest (Table 2) purification was found to be simple as the LCMS chromatograms were clean. Based on our results, active species **2** appears to be less reactive than some of the often used active esters (i.e., pentafluorophenyl or *p*-nitrophenyl) of carboxylic acids. This low reactivity could potentially become useful when reactive sites of multi-functionalized reagents need to be differentiated or when extremely reactive carboxylic acid substrates are used. Complex **2** derived from alkyl acids is more reactive (reactions slowly progress at rt) while aryl acids need prolonged heating for good conversion.

In summary, a versatile method for the synthesis of acyl ureas from acids and amines has been developed. The protocol enables the synthesis of diverse sets of acyl ureas from a vast commercially available reagent pool. In addition, we describe a mild method for the synthesis of amides. In the latter route, the Burgess reagent acts as a weak coupling reagent, which is of practical use especially for highly reactive or unstable carboxylic acids.

Supplementary data

The following supplementary data is available: experimental details, representative LCMS chromatograms, NMR spectra for all new compounds, and characterization of **2a**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.015.

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