Organic LETTERS

Letter

pubs.acs.org/OrgLett

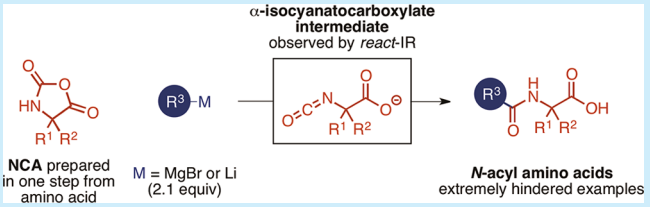
Synthesis of Sterically Hindered *N*-Acylated Amino Acids from *N*-Carboxyanhydrides

Gabriel Schäfer and Jeffrey W. Bode*

Laboratorium für Organische Chemie, Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir Prelog Weg 1-5, 8093 Zürich, Switzerland

Supporting Information

ABSTRACT: Sterically hindered *N*-acyl, *gem*-disubstituted amino acids are easily prepared via the addition of organometallic reagents to *N*-carboxyanhydrides (NCA). The process tolerates a wide variety of functional groups and allows the synthesis of amide products not readily accessible by traditional acylation chemistry. The existence of an isocyanate intermediate was established by *in situ* IR spectroscopy.

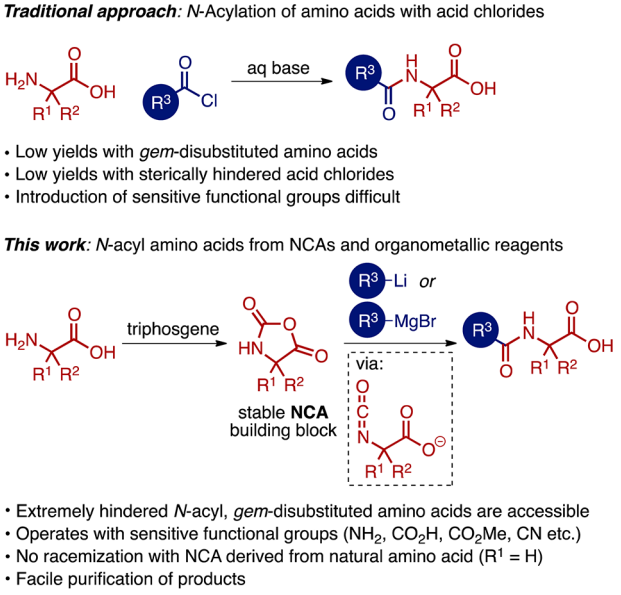


Amide bond formation is among the most prevalent and important reactions in organic synthesis.[1] The common method of preparing amides is the dehydrative coupling of amines with carboxylic acids by the action of a coupling agent.[2] Although this approach is routinely used, it is not without limitations.[3] The synthesis of sterically hindered amides can be cumbersome due to the slow attack of the amine onto the activated carboxylate. To address the formation of these important amide products, we recently reported the addition of Grignard reagents to isocyanates. Using this methodology, extremely hindered amides can be prepared with ease and in high yield.[4]

Our approach, however, was not suitable for the preparation of a key class of hindered amides, those derived from *gem*-disubstituted amino acids, due to the lack of a suitable isocyanate starting material. Recent advances in the construction of enantiomerically enriched disubstituted amino acids improve access to these building blocks,[5] but do not address the challenging acylation of these sterically hindered substrates. Traditionally, *N*-acyl substrates are prepared from the corresponding amino acid and an acid chloride under basic conditions.[6] This approach works well for sterically unbiased starting materials, but is usually low yielding for sterically hindered examples and incompatible with sensitive functional groups.[7]

We now report the clean and convenient formation of sterically hindered *N*-acyl, *gem*-disubstituted amino acids by the addition of Grignard or organolithium reagents to *N*-carboxyanhydrides (NCAs or Leuchs anhydrides). Our studies were inspired by literature reports on the use and properties of *N*-carboxyanhydrides in polymer chemistry.[8] NCAs are routinely used as starting materials in the preparation of polypeptides via ring-opening polymerization under basic conditions.[9] We postulated that it should be possible to prepare *N*-acylated amino acids in one step by adding 2 equiv of a Grignard reagent to an NCA. The first equivalent of the Grignard reagent would abstract the N–H proton leading to the formation of an α-isocyanatocarboxylate.[10] This transient intermediate would react with the second equivalent of the organometallic reagent to form the desired amide (Scheme 1).

Scheme 1. Acylation of Amino Acids

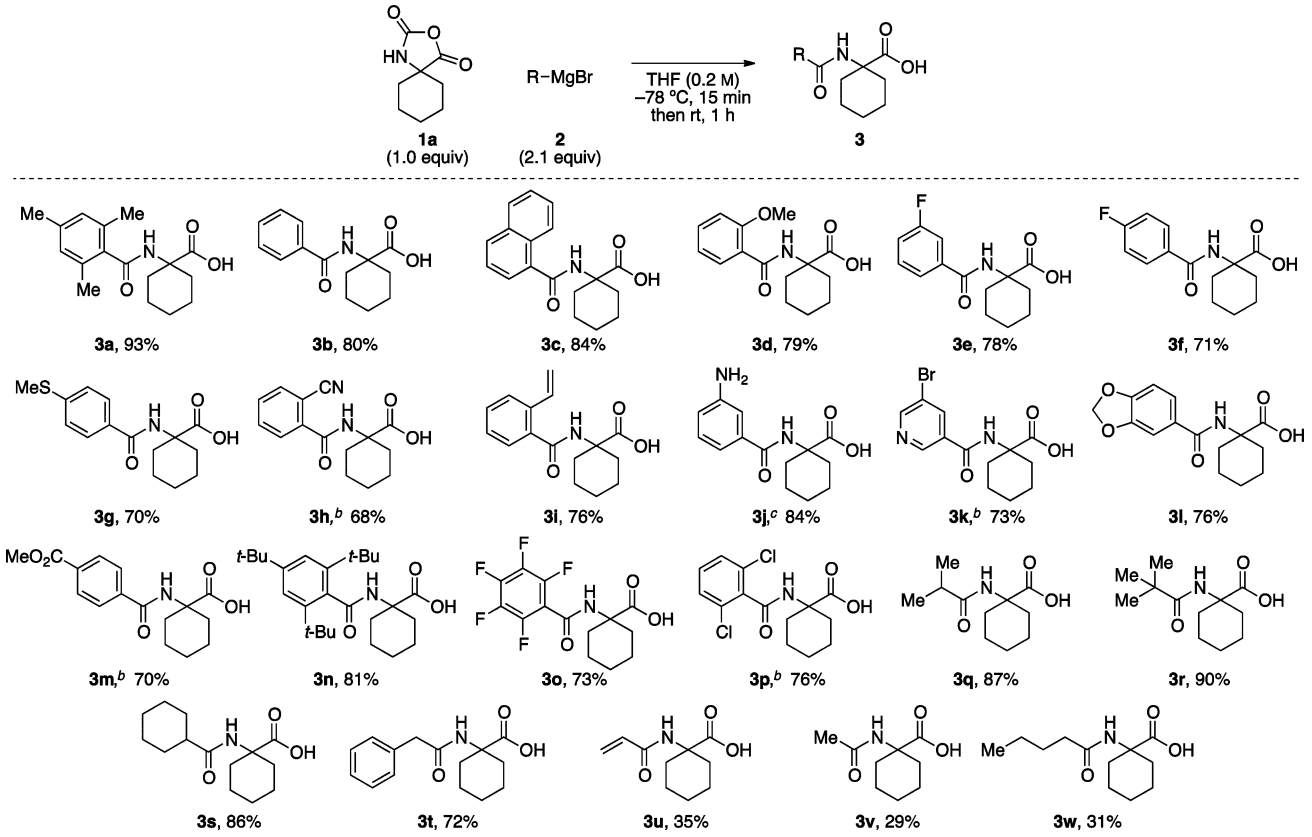


We began our investigation by the addition of a slight excess of mesitylmagnesium bromide to a solution of 3-oxa-1-azaspiro[4.5]decane-2,4-dione **1a** (cyclohexyl-NCA) in THF (Scheme 2). Only a complex mixture of products could be obtained when the Grignard reagent was introduced at 0 °C, most likely due to polymerization of the NCA starting material. Upon lowering the temperature to −78 °C, we obtained the desired product **3a** in very good yield. The isolation of the

Received: February 18, 2014
Published: February 26, 2014

dx.doi.org/10.1021/ol500523n | Org. Lett. 2014, 16, 1526–1529

Scheme 2. Addition of Various Grignard Reagents to Cyclohexyl-NCA (1a)[a]



[a]Isolated yields. **1a** (0.50 mmol), Grignard reagent **2** (1.05 mmol), THF (0.2 M), −78 °C, 15 min; rt, 1 h. [b] Grignard reagent prepared via Mg−Br exchange at low temperature before the NCA in THF (0.2 M) was added. [c] 3-[Bis(trimethylsilyl)amino]phenylmagnesium chloride was used.

product was simple; after aqueous workup, the crude material was washed with Et_2O to obtain the analytically pure *N*-acylated pure amino acid **3a**.

With the optimal conditions in hand, we explored the substrate scope of the Grignard reagent (Scheme 2). As anticipated from the results with mesitylmagnesium bromide, the reaction worked well with standard aromatic Grignard reagents to provide the corresponding products (**3b**−**g**) in high yields. Products containing sensitive functional groups such as nitrile (**3h**), ester (**3m**), or free amine (**3j**) were easily prepared, as well as products derived from pyridinyl (**2k**) and styrenyl (**2i**) Grignard reagents.[11] Many of these examples would be difficult to synthesize via traditional methods. Hindered Grignard reagents including pentafluorophenyl, 2,6-dichlorophenyl, isopropyl, or *tert*-butyl Grignard also provided the desired products (**3o**−**3r**). Even the extremely bulky 2,4,6-tri-*tert*-butylphenyl Grignard reagent could be used to cleanly afford sterically congested amide **3n**.

The reaction with 2 equiv of sterically unbiased, aliphatic Grignard reagents was problematic; only moderate yields of the corresponding products (**3u**−**w**) could be isolated. We attributed the low yield to a competing nucleophilic attack of the Grignard reagent to the anhydride carbonyl C5, which would lead to ring opening of the NCA followed by polymerization.

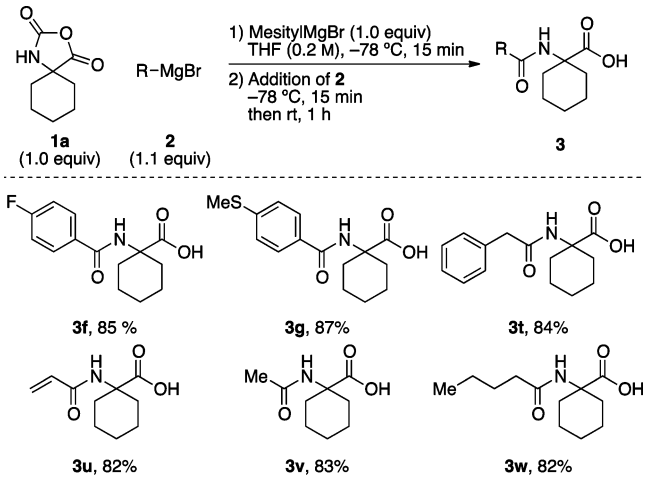
We hypothesized that the addition of a sterically hindered Grignard reagent to an NCA at low temperature could selectively generate the intermediate isocyanate (*vida infra*), which could then be trapped by a second, less hindered organometallic reagent. Indeed, when cyclohexyl-NCA **1a** was treated with 1.0 equiv of mesityl Grignard, followed by the addition of 1.1 equiv of a second Grignard reagent **2**, only the product stemming from Grignard reagent **2** was observed. Using this modified procedure, we could increase the yield of several products derived from sterically unbiased Grignard reagents (see Scheme 3 in comparison to Scheme 2).

Encouraged by the success of the addition of Grignard reagents to NCAs, we also investigated the use of organolithium reagents in this amide-forming methodology. Due to the instability of most organolithium reagents at room temperature, we modified the addition sequence: the organolithium species was generated at low temperature, followed by the addition of the NCA in THF at −78 °C (Scheme 4). Using this reverse addition protocol several interesting heterocyclic amides could be prepared in good yields (**5a**−**e**). In addition, lithium acetylide (**5f**) and lithium enolate (**5g**) were feasible substrates. It was also possible to use *ortho*-lithiated arenes bearing protected alcohols, free acids, amides, and sulfonamides as nucleophiles; the corresponding *N*-acyl amino acids (**5h**−**k**) were isolated in high yields.

The scope of the NCA was found to be equally broad (Scheme 5). NCAs derived from aliphatic, *gem*-disubstituted amino acids were excellent substrates, and a wide range of different products could be prepared (**6a**−**f**). Products containing aromatic side chains (**6h**−**i**) were also accessible. Furthermore, our methodology allowed for the synthesis of a *N*-acylated α,β-dehydroamino acid (**6g**). Heteroatom containing NCAs also cleanly reacted with Grignard reagents to

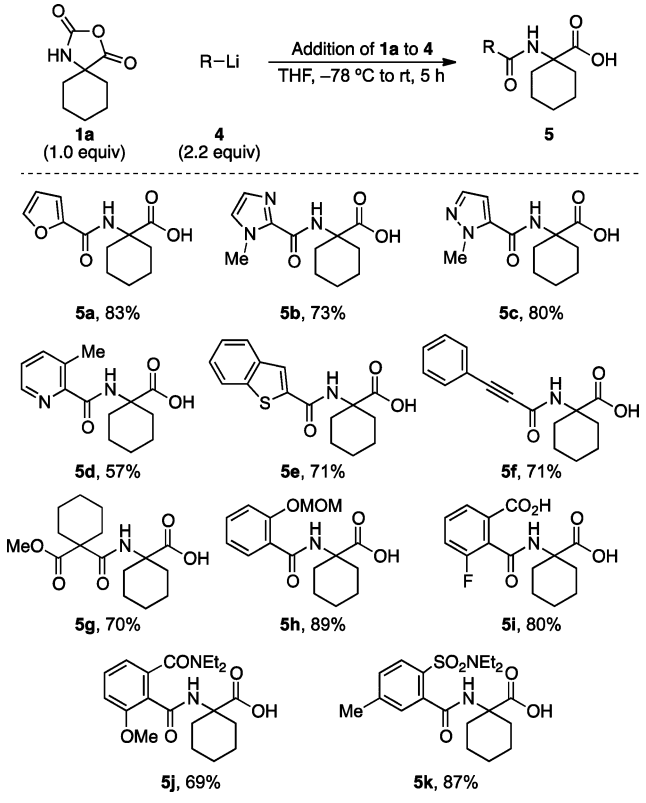
dx.doi.org/10.1021/ol500523n | *Org. Lett.* 2014, 16, 1526−1529

Scheme 3. Addition of Grignard Reagents (2) to Cyclohexyl-NCA (1a) Using Mesitylmagnesium Bromide As a Sacrificial Base[a]



[a]Isolated yields. **1a** (0.50 mmol), Grignard reagent **2** (1.05 mmol), THF (0.2 M), −78 °C, 15 min; rt, 1 h.

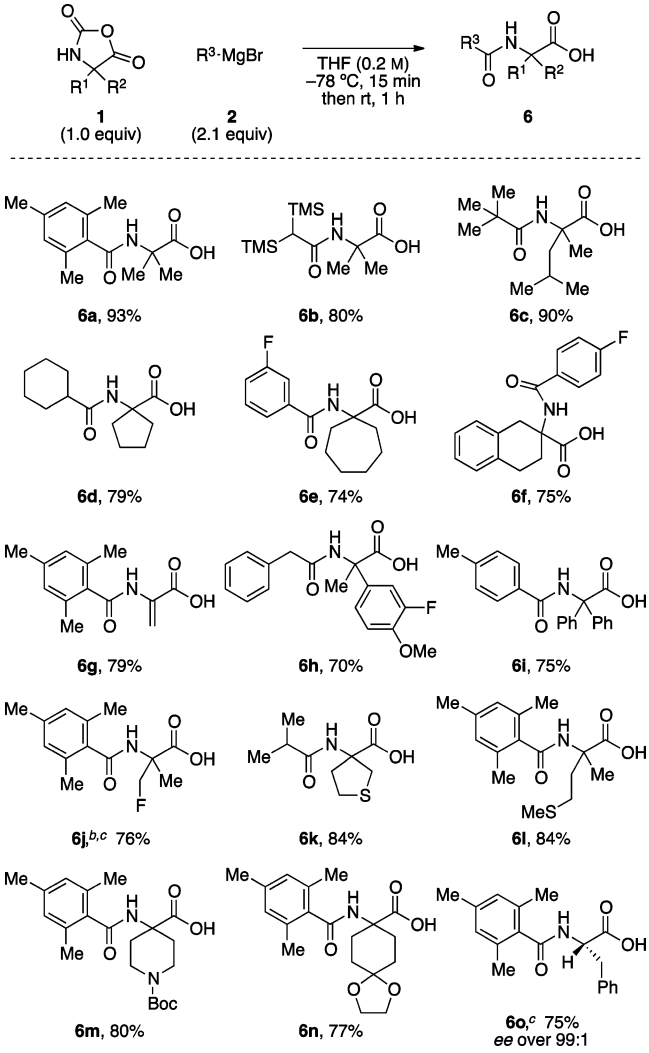
Scheme 4. Addition of Organolithium Reagents (4) to Cyclohexyl-NCA (1a)[a]



[a]Isolated yields. *In situ* generation of **4** (2.2 equiv), then addition of **1a** (0.50 mmol) in THF (0.2 M), −78 °C to rt, 5 h.

provide the corresponding products in high yields (**6j**–**n**). Interestingly, product **6j** was prone to fluoride elimination. This side reaction was suppressed by the addition of TMSCl prior to the introduction of the Grignard reagent. Finally, we investigated the addition of mesitylmagnesium bromide to an enantiopure NCA and obtained *N*-acylated amino acid **6o** without racemization.

Scheme 5. Addition of Grignard Reagents (2) to *gem*-Disubstituted NCAs (1)[a]



[a]Isolated yields. **1** (0.50 mmol), Grignard reagent **2** (1.05 mmol), THF (0.2 M), −78 °C, 15 min; rt, 1 h. [b] TMSCl (1.05 equiv) was added. [c] −78 °C to rt, 5 h.

In order to establish the existence of an intermediate α-isocyanatocarboxylate we followed the reaction by *react*-IR. Isocyanates are known to have a strong, isolated absorption band at 2250 cm^{-1}. Upon addition of mesitylmagnesium bromide (2.1 equiv) to a solution of cyclohexyl-NCA **1a** (1.0 equiv) at −78 °C, an absorption band at 2250 cm^{-1} appeared immediately, consistent with the formation of an intermediate isocyanate (Figure 1). To our surprise, this isocyanate was stable at −78 °C, even in the presence of unreacted Grignard reagent. Only upon warming of the reaction mixture was the isocyanate consumed by the second equivalent of the Grignard reagent to form the amide product.[12]

An advantage of this methodology is that the NCA substrates are readily prepared in one step from the amino acid and triphosgene and, if necessary, amenable to column chromatography.[13] The NCAs are easily handled compounds that can be stored for months without any sign of decomposition (see Supporting Information for further information).

In summary, we have identified a new approach to the synthesis of *N*-acyl, *gem*-disubstituted amino acids by the

dx.doi.org/10.1021/ol500523n | *Org. Lett.* 2014, 16, 1526–1529

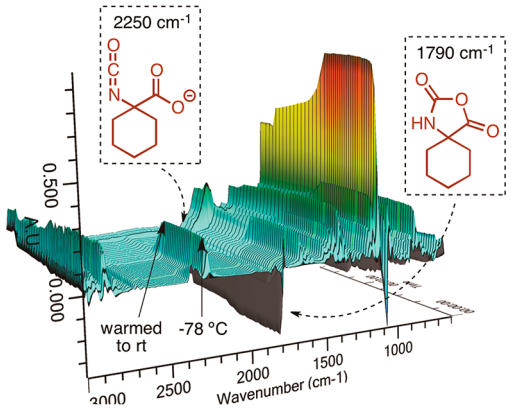


Figure 1. *React*-IR differential spectrum.

addition of organometallic reagents to *N*-carboxyanhydrides (NCA). The reaction proceeds via an intermediate α-isocyanatocarboxylate, whose existence was demonstrated by *react*-IR. This method is compatible with a wide range of functional groups and the use of enantiomerically pure amino acid derived NCAs.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bode@org.chem.ethz.ch.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by ETH Research Grant ETH-12 11-1. We thank the ETH Mass Spectroscopy Service for high-resolution mass spectrometry data, Claudio Grünenfelder (group Prof. Helma Wennemers, ETH) for assistance with *react*-IR measurements, and Lukas Leu (ETH) for experimental assistance.

■ REFERENCES

(1) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451−3479.
(2) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606−631.
(3) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471−479.
(4) Schäfer, G.; Matthey, C.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9173−9175.
(5) (a) Reeves, J. T.; Tan, Z.; Herbage, M. A.; Han, Z. S.; Marsini, M. A.; Li, Z.; Li, G.; Xu, Y.; Fandrick, K. R.; Gonnella, N. C.; Campbell, S.; Ma, S.; Grinberg, N.; Lee, H.; Lu, B. Z.; Senanayake, C. H. *J. Am. Soc. Chem.* **2013**, *135*, 5565−5568. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229. (c) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867−870. (d) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276−9286. (e) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708−2748.
(6) (a) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2451−2471. (b) Ronwin, E. *J. Org. Chem.* **1953**, *18*, 1546−1553.
(7) An alternative approach towards sterically hindered *N*-acylated Aib-derivatives was disclosed by Obrecht and Heimgartner. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1987**, *70*, 102−115.
(8) Seminal work: (a) Leuchs, H. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 857−861. (b) Leuchs, H.; Manasse, W. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 3235−3249. (c) Leuchs, H.; Geiger, W. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1721−1726.
(9) Selected reviews: (a) Kricheldorf, H. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 5752−5784. (b) Hadjichristidis, N.; Iatrou, H.; Pitsikalis, M.; Sakellariou, G. *Chem. Rev.* **2009**, *109*, 5528−5578. (c) Deming, T. J. *Adv. Mater.* **1997**, *9*, 299−311.
(10) α-Isocyanatocarboxylic acids were speculated to be intermediates in base initiated NCA polymerizations. However, several studies excluded their existence, e.g. Kricheldorf treated Bn-Glu NCA with the strong base HMDS, but no isocyanate absorption could be observed by FTIR. Kricheldorf, H. R.; Greber, G. *Chem. Ber.* **1971**, *104*, 3131−3145.
(11) The majority of Grignard reagents bearing sensitive functional groups were prepared according to: Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333−3336.
(12) We cannot completely rule out the possibility that the isocyanate is only a resting state of the reaction and the amide formation proceeds via a different mechanism.
(13) Daly, W. H.; Poché, D. *Tetrahedron Lett.* **1988**, *29*, 5859−5862.