Amide Formation

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Facile Synthesis of Sterically Hindered and Electron-Deficient Secondary Amides from Isocyanates**

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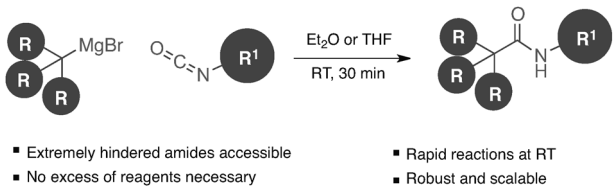
Amide bond formation is widely regarded as the most used chemical reaction in drug discovery.[1] Despite the importance of amides, nearly all are formed by reactions operating under a single mechanistic approach: dehydrative condensation of amines and carboxylic acids by the action of a coupling agent.[2] This approach has proven to be highly suitable, albeit often wasteful and expensive, for the majority of amides.[3] An exception is the preparation of highly hindered and electron-deficient amides, for which difficulty in their formation by condensation is well known.[4] Although a number of mechanistically unique amide bond forming reactions have been reported,[5] including work from our own labs,[6] none of these new reactions addresses the challenge of preparing amides from hindered acids or those derived from bulky or electron-deficient amines.

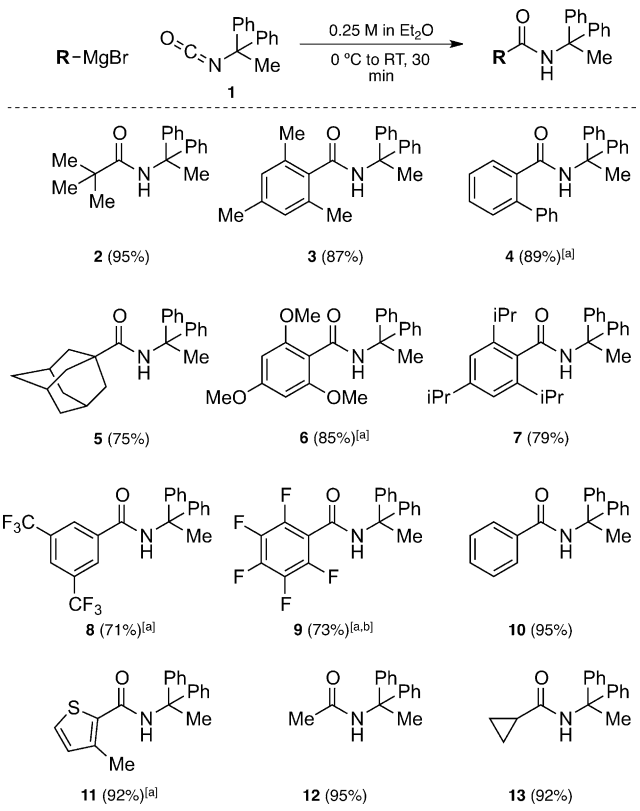
As part of our research program aimed at the identification and development of new amide-forming reactions, we have been seeking approaches to the preparation of hindered amides and those derived from electron-deficient amines. We now document a rapid and simple approach to such targets by the addition of Grignard reagents to hindered isocyanates (Scheme 1). The reactions proceed in minutes at room temperature, tolerate a number of functional groups, and provide access to hindered secondary amides not readily prepared by standard methods.



Scheme 1. Synthesis of sterically hindered and electron-deficient amides by direct coupling of Grignard reagents to isocyanates.

Since the elegant work of Gilman on the titration of organomagnesium halides through addition to isocyanates,[7] only scattered applications of this reaction have appeared.[8] To the best of our knowledge, a general protocol for the addition of bulky Grignard reagents to bulky or electron-deficient isocyanates has not been reported.[9] More recently, rhodium-catalyzed additions of organostannanes[10] and boronic acids[11] to isocyanates were disclosed but—despite the convenience of these starting materials—these methods require an expensive rhodium catalyst and have only been applied to unhindered substrates.

Using **1** as a model substrate, we explored the addition of various Grignard reagents to this hindered isocyanate (Scheme 2). We found that the reactions could be conducted under a variety of conditions, and selected Et_2O as a solvent for further exploration of the substrate scope. Addition of the Grignard reagent (as a solution in Et_2O or THF, 1.0 equiv) to the isocyanate (0.25 M in Et_2O, 1.0 equiv) at 0 °C followed by warming to room temperature was found to be applicable to nearly all substrates examined.[12] In most cases, aqueous



Scheme 2. Grignard additions to isocyanate **1**. Reaction conditions: **1** (1.0 mmol), Grignard reagent (1.0 mmol), Et_2O (4 mL), 0 °C to RT, 30 min. [a] In situ formation of Grignard reagent from corresponding bromide and Mg metal. [b] 3 h reaction time.

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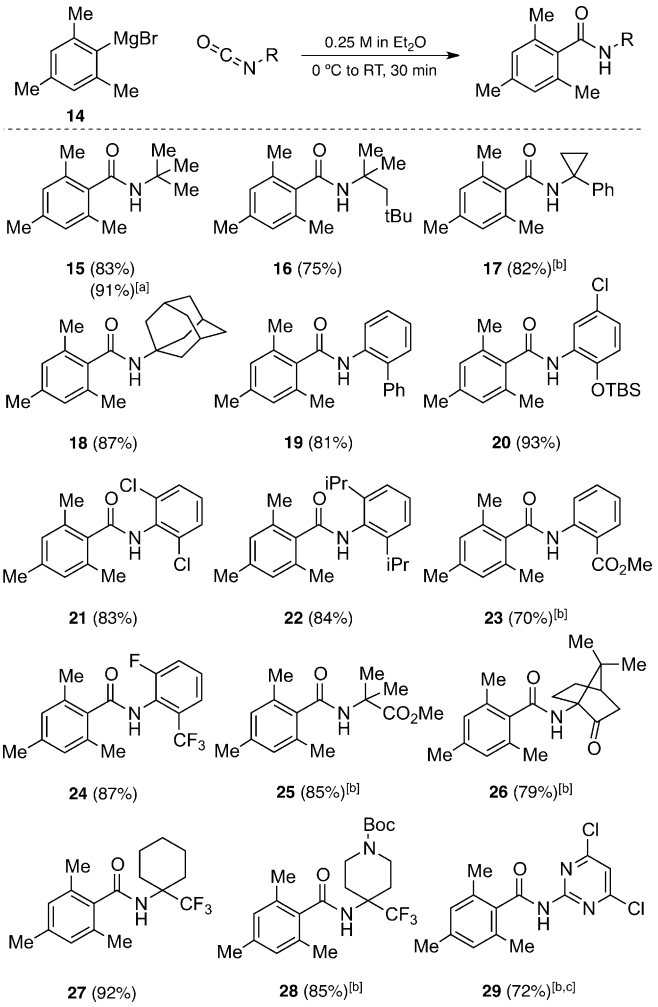
workup and washing of the crude material with hexanes provided analytically pure amide products without the need for further purifications.

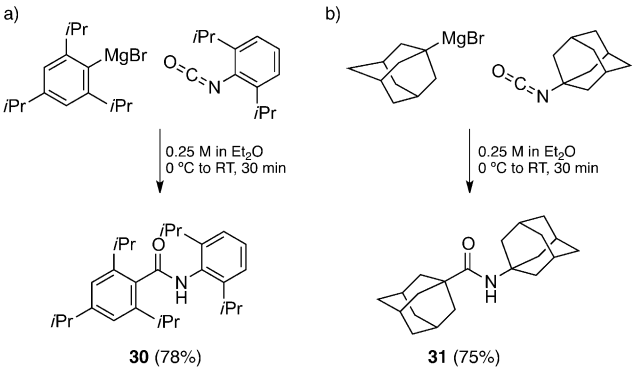
Hindered Grignard reagents including *tert*-butyl, mesityl and 2-biphenyl Grignard cleanly added to the isocyanate to give amide products **2**–**4** in excellent yield. Even the extremely bulky adamantyl-, 2,4,6-trimethoxyphenyl and 2,4,6-triisopropylphenyl Grignard reagents provided desired products **5**–**7** in good yield. As anticipated from these results, several other amides derived from aromatic (**8**–**10**), heterocyclic (**11**) and aliphatic (**12**, **13**) Grignards were easily prepared by this protocol. In no instance did we observe overreaction of the Grignard reagent with the resulting amide; this proved to be the case even when less hindered substrates were used.

The scope of the isocyanate was found to be equally broad (Scheme 3). Hindered isocyanates such as *tert*-butyl, *tert*-octyl, 1-phenylcyclopropyl, or adamantyl isocyanate were excellent substrates and delivered amide products **15**–**18** in high yields. Amide **15** was synthesized on a 15 mmol scale using 2-methyl THF as a more industry-friendly solvent.[13] The synthesis of amides from electron-deficient amines by couplings with activated esters is often challenging due to their decreased nucleophilicity. In contrast, electron-deficient isocyanates are excellent substrates for the reaction with Grignard reagents. Amide products **21**–**24** from bulky and electron-deficient, aromatic isocyanates, such as 2,6-dichlorophenyl, 2,6-diisopropylphenyl and 2-fluoro-6-trifluoromethylphenyl isocyanate were accessible. Furthermore, our conditions were applicable to the synthesis of hindered, electron-deficient, aliphatic amides **25**–**27** derived from amino-isobutyrate ester and trifluoromethyl-substituted isocyanates. The α-trifluoromethyl-substituted amides could serve as promising building blocks in medicinal chemistry.[14] The chemoselective addition of Grignard reagents to isocyanates bearing ester or ketone functional groups is noteworthy; the corresponding amides (**23**, **25**, **26**) were obtained in good yield.



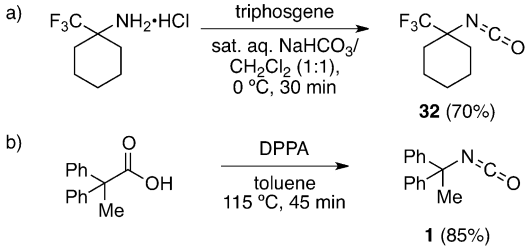
Scheme 3. Mesityl Grignard (**14**) addition to various isocyanates. Reaction conditions: isocyanate (1.0 mmol), mesityl Grignard (**14**, 1.0 mL of 1 M solution in Et_2O), Et_2O (4 mL), 0 °C to RT, 30 min. [a] Reaction performed on 15 mmol scale in 2-MeTHF (60 mL). [b] −78 °C to RT, 30 min. [c] Isocyanate prepared in situ from 4,6-dichloropyrimidin-2-amine and oxalyl chloride in benzene.

Even the combination of the most hindered substrates from each reaction partner gave the expected amide in good yield, allowing for the preparation of exceptionally hindered secondary amides **30** and **31** (Scheme 4).[15]



Scheme 4. Synthesis of sterically hindered amides **30** and **31**.

The hindered isocyanate substrates are readily prepared from either amines or carboxylic acids using well-established methods and, if necessary, amenable to column chromatography.[16] Two examples are shown in Scheme 5. These isocyanates are easily handled compounds that can be stored for months without any sign of decomposition; many of them are commercially available. The Grignard reagents



Scheme 5. Synthesis of isocyanates from a) amines and b) carboxylic acids. DPPA = Diphenylphosphoryl azide.

used in this study were either commercially available or readily prepared from the corresponding organohalide and magnesium metal. We anticipate that other methods for Grignard formation, such as magnesium–halogen exchange[17] or transmetalation from boron reagents,[18] will also be suitable for this chemistry. The use of other organometallic species, perhaps with the aid of a catalyst, is also likely to be viable.

In summary, we have identified a convenient and rapid approach to the synthesis of hindered and electron-deficient amides by the direct coupling of isocyanates with Grignard reagents. This provides a reliable solution to the preparation of amides for which traditional, coupling reagent based reactions generally fail to give the desired product. The starting materials, while not as common as amines and carboxylic acids, are readily obtained by well-known protocols. We anticipate that our method will be of considerable use for the preparation of challenging amides and will find application in the synthesis of pharmaceuticals and materials.

Experimental Section

Typical procedure for the preparation of **27**: In a flame-dried Schlenk-flask under N_2 1-isocyanato-1-(trifluoromethyl)cyclohexane (0.19 g, 1.0 mmol) was dissolved in dry Et_2O (4 mL) and cooled to 0 °C. Mesitylmagnesium bromide (**14**, 1.0 mL of a 1 M solution in Et_2O) was added dropwise over 2–3 min and the reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and stirred for 1–2 min before EtOAc (25 mL) was added and the phases separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was washed with hexanes, the solid was collected by filtration and dried under high vacuum to obtain the pure product **27** as a colorless solid (0.29 g, 0.92 mmol, 92 %).

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[1] S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451 – 3479.
[2] E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606 – 631.
[3] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, J. Russell, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaksh, T. Zhang, *Green Chem.* **2007**, *9*, 411 – 420.
[4] V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471 – 479.
[5] a) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790 – 792; b) X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 5446 – 5448; c) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796 – 13797; d) B. Shen, D. M. Makley, J. N. Johnston, *Nature* **2010**, *465*, 1027 – 1032; e) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196 – 4197; f) N. Shangguan, S. Katukojvala, R. Greenberg, L. J. Williams, *J. Am. Chem. Soc.* **2003**, *125*, 7754 – 7755; For further references on new amide bond forming reactions, see Ref. [4].
[6] a) J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem.* **2006**, *118*, 1270 – 1274; *Angew. Chem. Int. Ed.* **2006**, *45*, 1248 – 1252; b) J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798 – 13799; c) V. R. Pattabiraman, A. O. Ogunkoya, J. W. Bode, *Angew. Chem.* **2012**, *124*, 5204 – 5208; *Angew. Chem. Int. Ed.* **2012**, *51*, 5114 – 5118; d) A. M. Dumas, G. A. Molander, J. W. Bode, *Angew. Chem.* **2012**, *124*, 5781 – 5784; *Angew. Chem. Int. Ed.* **2012**, *51*, 5683 – 5686.
[7] a) H. Gilman, C. R. Kinney, *J. Am. Chem. Soc.* **1924**, *46*, 493 – 497; b) H. Gilman, M. Furry, *J. Am. Chem. Soc.* **1928**, *50*, 1214 – 1216.
[8] a) H. M. Singleton, W. R. Edwards, Jr., *J. Am. Soc. Chem.* **1938**, *60*, 540 – 544; b) L. Field, J. E. Lawson, J. W. McFarland, *J. Am. Chem. Soc.* **1956**, *78*, 4389 – 4394; c) J. W. McFarland, R. L. Harris, *J. Org. Chem.* **1967**, *32*, 1273 – 1274; d) K. A. Parker, E. G. Gibbons, *Tetrahedron Lett.* **1975**, *16*, 981 – 984; e) Y. Zhang, J. Jiang, Y. Chen, *Tetrahedron Lett.* **1987**, *28*, 3815 – 3816; f) I. Stefanuti, S. A. Smith, R. J. K. Taylor, *Tetrahedron Lett.* **2000**, *41*, 3735 – 3738; g) A. Padwa, K. R. Crawford, P. Rashatasakhon, M. Rose, *J. Org. Chem.* **2003**, *68*, 2609 – 2617; h) M. I. Antczak, J. M. Ready, *Chem. Sci.* **2012**, *3*, 1450 – 1454.
[9] The use of organometallic reagents for the preparation of sterically hindered compounds is well established: a) Preparation of tetra-*ortho*-substituted biaryl naphthalenes with organolithium species: A. C. Glass, S. Klonoski, L. N. Zakharov, S.-Y. Liu, *Chem. Commun.* **2011**, *47*, 286 – 288; b) Bulky Grignard reagents in the synthesis of sterically demanding ligands: A. Labonne, T. Kribber, L. Hintermann, *Org. Lett.* **2006**, *8*, 5853 – 5856; c) Synthesis of new biarylphosphine ligands with sterically hindered Grignard reagents: L. Salvi, N. R. Davis, S. Z. Ali, S. L. Buchwald, *Org. Lett.* **2012**, *14*, 170 – 173.
[10] T. Koike, M. Takahashi, N. Arai, A. Mori, *Chem. Lett.* **2004**, *33*, 1364 – 1365.
[11] T. Miura, Y. Takahashi, M. Murakami, *Chem. Commun.* **2007**, 3577 – 3579.
[12] For isocyanates with sensitive functional groups (ester, ketone or carbamates) reaction was cooled to −78 °C and after the addition of the Grignard reagent warmed to RT.
[13] T. Laird, *Org. Process Res. Dev.* **2012**, *16*, 1 – 2.
[14] J. M. Axten (Glaxo Group Limited), WO2004/002490A2, **2004**.
[15] For rare examples of the synthesis of sterically hindered secondary amides, see: a) Y. Rao, X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2009**, *131*, 12924 – 12926; b) H. Kurata, K. Ishibashi, K. Kojima, *Synlett* **1996**, 517 – 518; c) P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1987**, *70*, 354 – 368; d) K. Sasaki, D. Crich, *Org. Lett.* **2011**, *13*, 2256 – 2259; e) M. Inoue, N. Shinohara, S. Tanabe, T. Takahashi, K. Okura, H. Itoh, Y. Mizoguchi, M. Iida, N. Lee, S. Matsuoka, *Nat. Chem.* **2010**, *2*, 280 – 285.
[16] Selected examples: a) Synthesis of isocyanates from amine hydrochloride salts: J. H. Tsai, L. R. Takaoka, N. A. Powell, J. S. Nowick, *Org. Synth.* **2002**, *78*, 220 – 222; b) Synthesis of isocyanates from carboxylic acids: C. Spino, M.-A. Joly, C. Godbout, M. Arbour, *J. Org. Chem.* **2005**, *70*, 6118 – 6121.
[17] a) A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396 – 3399; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333 – 3336; b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem.* **2006**, *118*, 165 – 169; *Angew. Chem. Int. Ed.* **2006**, *45*, 159 – 162; c) A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem.* **2006**, *118*, 511 – 515; *Angew. Chem. Int. Ed.* **2006**, *45*, 497 – 500.
[18] M. A. Reichle, B. Breit, *Angew. Chem.* **2012**, *124*, 5828 – 5832; *Angew. Chem. Int. Ed.* **2012**, *51*, 5730 – 5734.

Communications

Amide Formation

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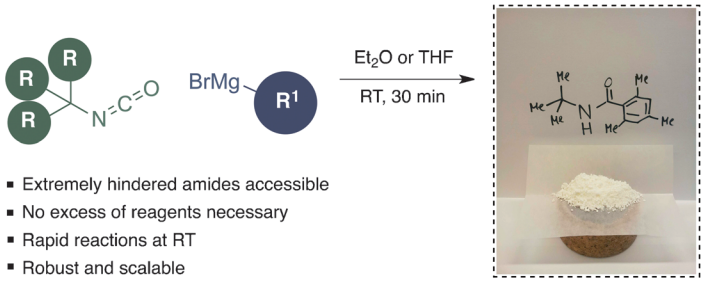
Facile Synthesis of Sterically Hindered and Electron-Deficient Secondary Amides from Isocyanates



- Extremely hindered amides accessible
- No excess of reagents necessary
- Rapid reactions at RT
- Robust and scalable

The big easy: The direct coupling of Grignard reagents to isocyanates provides a facile and robust solution for the synthesis of sterically hindered and electron-deficient secondary amides. The products are obtained in high yields without the need for excess reagents or chromatographic purification.