J|A|C|S
COMMUNICATIONS

Published on Web 12/05/2008

Amide Synthesis from Alcohols and Amines by the Extrusion of Dihydrogen

Lars Ulrik Nordstrøm, Henning Vogt, and Robert Madsen*

Center for Sustainable and Green Chemistry, Department of Chemistry, Building 201, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark

Received October 15, 2008; E-mail: rm@kemi.dtu.dk

The amide bond is one of the most important linkages in organic chemistry and constitutes the key functional group in peptides, polymers, and many natural products and pharmaceuticals.[1] Amides are usually prepared by coupling of carboxylic acids and amines by the use of either a coupling reagent[2] or by prior conversion of the carboxylic acid into a derivative.[3] Alternative procedures include the Staudinger ligation,[4] aminocarbonylation of aryl halides,[5] and oxidative amidation of aldehydes.[6] However, all these methods require stoichiometric amounts of various reagents and lead to equimolar amounts of byproducts. In special cases, amides can be formed by catalytic procedures as shown for the Schmidt reaction between ketones and azides,[7] the Beckmann rearrangement,[8] and the amidation of thioacids with azides.[9]

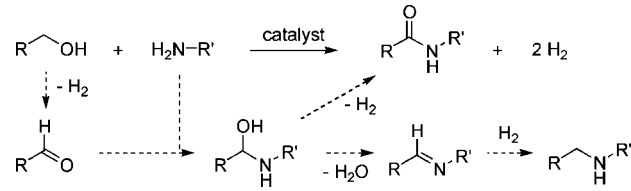
A more environmentally friendly protocol for amide synthesis is the direct amidation of amines with alcohols where two molecules of dihydrogen are liberated (Scheme 1). This unique transformation has only been described once before where a ruthenium pincer complex was used for the direct coupling of sterically unhindered primary amines and alcohols.[10] Presumably, the reaction proceeds through the intermediate aldehyde which reacts with the amine to give a hemiaminal that is subsequently dehydrogenated to the amide.[10] The last step of the mechanism is crucial since the hemiaminal may also eliminate water to generate an imine which can undergo hydrogenation with the liberated dihydrogen to form an amine. In fact, alkylation of amines with alcohols has been described with several ruthenium and iridium catalysts[11] and we have recently used this protocol for synthesis of piperazines from 1,2-diols and amines.[12]

In a study of new ruthenium catalysts for the alkylation of amines with alcohols we investigated various *N*-heterocyclic carbenes (NHC)[13] as ligands. Unexpectedly, we observed exclusive formation of amides in these reactions and none of the corresponding amines. Herein, we report the discovery of this new catalyst system for the direct synthesis of amides from alcohols and amines.

The first experiment was carried out with 2-phenylethanol, benzylamine, and 5% of the catalyst in refluxing toluene. The catalyst was generated *in situ* from $Ru(PPh_3)_3Cl_2$, imidazolium salt **A**, and potassium *tert*-butoxide where the latter deprotonates **A** to generate the corresponding carbene[13] (Figure 1).

The reaction afforded *N*-benzyl 2-phenylacetamide in 15% isolated yield after 16 h with a significant amount of alcohol and amine still remaining (Table 1, entry 1). None of the amide was formed in the absence of the carbene and the yield did not improve by changing the solvent, the temperature, or the ratio between the ruthenium complex and the carbene. The ruthenium precatalyst was therefore replaced with $Ru(COD)Cl_2$ in order to investigate the influence of the phosphine ligand. In the absence of phosphines no amide was observed (entry 2). Monodentate phosphine ligands with a larger cone angle than triphenylphosphine afforded a slightly better yield of the amide (entries 3−6) while bidentate phosphine ligands resulted in no reaction.[14] The carbene precursors were then changed

Scheme 1. Amide Formation from Alcohols and Amines



and this proved to have a more decisive impact on the amidation (entries 8−14). Unsaturated carbenes with aliphatic *N*-substituents gave significantly better yields with **D** as the best result while the corresponding saturated carbenes derived from **F**−**H** all gave lower yields. The phosphine ligand was investigated again and it was found that tricyclopentylphosphine ($PCyp_3$) gave a minor improvement (entries 15−19). For general use it was decided to utilize the more stable and crystalline HBF_4 salt (entry 19) which gave the same isolated yield of the amide as the free phosphine.

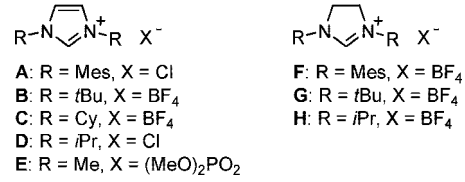
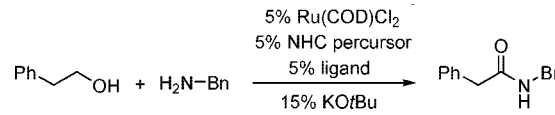


Figure 1. NHC precursors.

Table 1. Amidation with Different NHC and Phosphine Ligands[a]

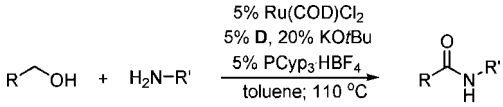


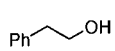
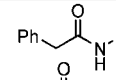
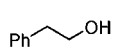
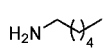
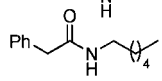
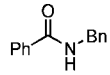
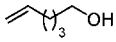
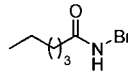
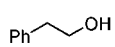
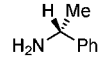
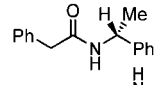
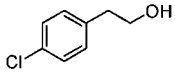
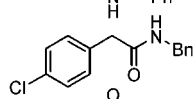
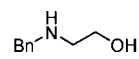
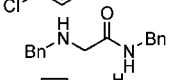
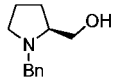
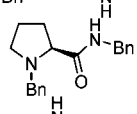
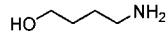
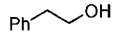
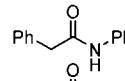
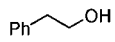
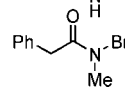
entry	NHC precursor	ligand	yield[b]
1	**A**		15%[c]
2	**A**	none	0%
3	**A**	PPh_3	21%
4	**A**	P(*o*-tol)$_3$	26%
5	**A**	PCy_3	27%
6	**A**	P*t*Bu$_3$	22%
7	**A**	P*n*Bu$_3$	9%
8	**B**	PCy_3	68%
9	**C**	PCy_3	84%
10	**D**	PCy_3	92%
11	**E**	PCy_3	53%
12	**F**	PCy_3	45%
13	**G**	PCy_3	22%
14	**H**	PCy_3	48%
15	**D**	PCy_2Ph	54%
16	**D**	PCy_2(*o*-biphenyl)	90%
17	**D**	P*t*Bu$_2$(*o*-biphenyl)	34%
18	**D**	$PCyp_3$	98%
19	**D**	$PCyp_3 \cdot HBF_4$	92%[d]

[a] In toluene at 110 °C; 24 h. [b] GC-yield. [c] Isolated yield from reaction with 5% of $Ru(PPh_3)_3Cl_2$. [d] Run using 20% of KO*t*Bu.

10.1021/ja808129p CCC: $40.75

Table 2. Amidation of Amines with Alcohols



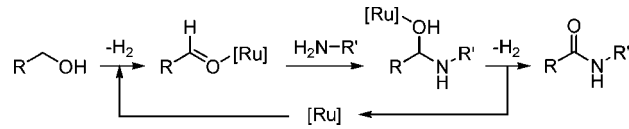
Entry	Alcohol	Amine	Amide	Yield[a]
1				93%[b]
2				100%[b]
3				78%
4				60%
5				70%
6				83%[b]
7				90%
8				60%
9				65%
10				21%[c]
11				40%[c]

[a] Isolated yield. [b] Ru(COD)Cl_2 (2%), ligands (2%), and base (8%). [c] In mesitylene at 163 °C.

With these optimized conditions in place the scope and limitation of the method could now be explored. A range of different primary alcohols were reacted with primary amines to afford the corresponding secondary amides in 60−100% isolated yield (Table 2, entries 1−9).

Sterically unhindered alcohols and amines gave the amide in high yield (entry 1 and 2). Benzyl alcohol was converted into benzamide (entry 3) while hex-5-en-1-ol gave the hexanamide with concomitant reduction of the olefin (entry 4). An optically pure amine could be employed and the product showed no sign of racemization according to optical rotation (entry 5). An aryl chloride also participated in the amidation (entry 6) while essentially no reaction occurred with the corresponding aryl bromide (data not shown). *N*-Benzylethanolamine could be coupled with benzylamine in high yield (entry 7) which shows that the transformation is selective for a primary amine. Optically pure *N*-benzyl-L-prolinol was converted into *N*,*N*′-dibenzyl-L-prolinamide with no sign of epimerization (entry 8). The amidation could also be carried out in an intramolecular fashion as illustrated with the formation of γ-butyrolactam (entry 9). Aniline and secondary amines, on the other hand, did not react with primary alcohols at 110 °C. However, when the temperature was raised to 163 °C complete conversion of the alcohol was observed. At this temperature, aniline and *N*-methylbenzylamine gave the amide in low to moderate yield while the remaining portion of the alcohol underwent self-condensation into the corresponding ester (entry 10 and 11).

Scheme 2. Mechanism for Ruthenium-Catalyzed Amide Formation



The amidation presumably follows the mechanism in Scheme 2 and does not proceed through an intermediate ester. The latter was confirmed by treating 2-phenylethyl 2-phenylacetate with benzylamine and the catalyst, which afforded none of the amide in Table 2, entry 1. The reaction between benzaldehyde and benzylamine under the same conditions led to exclusive formation of the corresponding imine and neither amide nor amine was observed. The imine does not react in the presence of the catalyst and this did not change by adding water or by conducting the reaction under a dihydrogen atmosphere. Imine formation has never been detected by GC in any of the experiments in Table 2. This indicates that the reaction proceeds through an aldehyde, but that the aldehyde stays coordinated to the metal (Scheme 2). Subsequent attack by the amine affords the hemiaminal which also stays coordinated to the metal. The amide is then formed after β-hydride elimination and at no time is a free aldehyde or hemiaminal released from the catalyst since this would lead to the formation of an unreactive imine.

In conclusion, we have developed a novel method for the amidation of amines with alcohols. The reaction is performed with a simple catalyst prepared from a ruthenium precursor, an *N*-heterocyclic carbene and a phosphine ligand. This system presents new opportunities for the preparation of a key functional group in organic chemistry.

Acknowledgment. We thank the Danish National Research Foundation for financial support.

Supporting Information Available: General experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Cupido, T.; Tulla-Puche, J.; Spengler, J.; Albericio, F. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 768. (b) Bode, J. W. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765.
(2) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447.
(3) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.
(4) Köhn, M.; Breinbauer, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3106.
(5) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460.
(6) Chang, J. W. W.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1138.
(7) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146.
(8) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 3599.
(9) Kolakowski, R. V.; Shangguan, N.; Sauers, R. R.; Williams, L. J. *J. Am. Chem. Soc.* **2006**, *128*, 5695.
(10) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790.
(11) (a) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555. (b) Fujita, K.-i.; Yamaguchi, R. *Synlett* **2005**, 560.
(12) Nordstrøm, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034.
(13) Dragutan, V.; Dragutan, I.; Delaude, L.; Demonceau, A. *Coord. Chem. Rev.* **2007**, *251*, 765.
(14) The following bidentate phosphine ligands were investigated: dppe, dppp, dppb, and dppf.

JA808129P