JOC*Note*

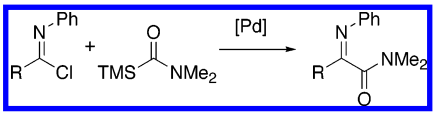
Palladium-Catalyzed Synthesis of α-Iminoamides from Imidoyl Chlorides and a Carbamoylsilane

Robert F. Cunico* and Rajesh K. Pandey

Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, Illinois 60115

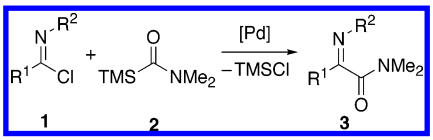
rfc@marilyn.chem.niu.edu

Received March 17, 2005



A series of pure imidoyl chlorides were converted into α-iminoamides by treatment with a carbamoylsilane under catalysis by palladium(0) complexes.

α-Aminoamides are important synthetic targets, as they represent the fundamental subunit of peptides and proteins. We[1] and others[2] have described methodologies which access such structures by directly establishing bond connectivity between the carbonyl and α-carbon atoms. Another entry, however, would be a two-step process in which similar establishment of connectivity would be followed by reduction of an α-imine function to generate the α-amino group. This approach would require the availability of α-iminoamides which, to our knowledge, have only been reported a few times in the chemical literature.[3] In both of these instances, the iminoamides were derived from previously extant carbon frameworks. We have recently had success in assembling α-ketoamides from the reaction of acid chlorides with a carbamoylsilane,[4] and report here on the analogous use of imidoyl chlorides (**1**) with a carbamoylsilane (**2**) to form α-iminoamides (**3**).[5]



Although the preparation and use of imidoyl chlorides have been reported frequently,[6] an examination of the literature indicated that few of these species had actually been isolated and characterized. Common precursors to **1** are secondary amides, and among the most typical reagents which have been employed for their conversion to imidoyl chlorides are PCl_5, phosgene, thionyl chloride, and triphenylphosphine−carbon tetrachloride.[7] However, for a given substitution pattern in **1**, the use of any one of these traditional preparative methods may give rise to various coproducts which may seriously impact the ability to isolate imidoyl chlorides in a pure state. Taken together with their hydrolytic instability, these factors have led in many instances to their preparation and use without intervening isolation. For the present purpose, imidoyl chlorides were required which were free of protonic impurities, as **2** is subject to ready protonolysis. We were thus drawn to a recently reported methodology for their preparation (and in situ use) that employed oxalyl chloride and 2,6-lutidine,[8,9] as we believed that removal of the attendant amine hydrochloride by filtration and subsequent distillation could afford pure imidoyl chlorides. We find that imidoyl chlorides (**1a**−**j**) bearing a fairly wide range of substitution patterns (R^1, R^2 = alkyl, aryl) may be prepared using this protocol and easily isolated as analytically pure materials by vacuum distillation. However, the imidoyl chlorides **1k**−**m** could not be prepared by the oxalyl chloride method, and were obtained by the use of PCl_5.[10] These results are shown in Table 1. Satisfactory analytical data were obtained for **1k** and **1*l***, but not for **1m**, whose spectral data and eventual conversion to **3m** confirmed its structure.

A preliminary investigation of reaction parameters for the conversion of **1e** to **3e** is given in Table 2. These data suggested a standard reaction profile under the mildest conditions which employed bis(tri-*tert*-butylphosphine)palladium(0) as catalyst in THF solvent at 60 °C. Positive results from exploring the full range of imidoyl chlorides prepared are summarized in Table 3. Attempts to use *N*-phenyl, *C*-aliphatic imidoyl chlorides bearing α-protons (**1**, R^1 = Me, nPr, iPr) led to the isolation of small yields (12−20%) of what spectral data indicated were impure imidoamides, possibly contaminated with the tautomeric enamines. When *N*-phenyl

(1) (a) Chen, J.; Cunico, R. F. *Tetrahedron Lett.* **2003**, *44*, 8025−8027. (b) Chen, J.; Cunico, R. F. *Tetrahedron Lett.* **2002**, *43*, 8595−8597.

(2) (a) Lin, Y.-S.; Alper, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 779−781. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210.

(3) (a) Masuda, K.; Adachi, J.; Nomura, K. *J. Chem. Soc., Perkin 1* **1981**, 1033−1036. (b) Lopatin, W.; Young, P. R., Jr.; Owen, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 960−969.

(4) Chen, J.; Cunico, R. F. *J. Org. Chem.* **2004**, *69*, 5509−5511.

(5) All **3** prepared were monoisomeric and are arbitrarily shown as the *Z* isomer.

(6) (a) Katritzky, A. R.; Hayden, A. E.; Kirichenko, K.; Pelphrey, P.; Ji, Y. *J. Org. Chem.* **2004**, *69*, 5108−5111 and references therein. (b) Kantlehner, W.; Mergen, W. W. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1995; Vol. 5, pp 654−660. (c) Kantlehner, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 6, pp 523−529. (d) Sustmann, R.; Korth, H. G. In *Methoden der Organische Chemie*; Thieme: Stuttgart, Germany, 1985; Vol. E5, pp 628−631. (e) Tennant, G. In *Comprehensive Organic Chemistry*; Pergamon: Oxford, UK, 1979; pp 469−487. (f) Bonnett, R. In *The Chemistry of the Carbon−Nitrogen Bond*; Patai, S., Ed.; Interscience: London, UK, 1970; Chapter 13. (g) Ulrich, H. *The Chemistry of Imidoyl Halides*; Plenum: New York, 1968.

(7) (a) Appel, R.; Warning, K.; Ziehn, K.-D. *Chem. Ber.* **1973**, *106*, 3450−3454. (b) This method has also been used to form imidoyl chlorides directly from mixtures of carboxylic acids and primary amines: Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32−35.

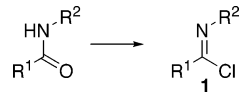
(8) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127−3129.

(9) The combination of oxalyl chloride and DMF has been used to produce an imidoyl chloride: Zhong, Y.-L.; Lee, J.; Reamer, R. A.; Askin, D. *Org. Lett.* **2004**, *6*, 929−931. The same reagents afford amidinium salts (Vilsmeier reagents) from tertiary amides (cf. Bosshard, H. H.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1659−1671).

(10) The use of PCl_5 for the preparation of **1** containing R = alkyl on the imide carbon atom did not afford pure imidoyl chlorides.

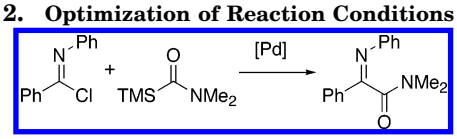
10.1021/jo050545h CCC: $30.25
Published on Web 05/20/2005

TABLE 1. Imidoyl Chlorides Prepared with Oxalyl Chloride (1a−j) and PCl_5 (1k−m)



	R^1	R^2	yield (%)
1a	Me	Ph	70
1b	^{i}Pr	Ph	76
1c	nPr	Ph	80
1d	tBu	Ph	72
1e	Ph	Ph	90
1f	4-MeOPh	Ph	90
1g	4-CNPh	Ph	85
1h	nPr	CH(Me)Ph	85
1i	tBu	CH(Me)Ph	80
1j	Ph	CH(Me)Ph	74
1k	2-furyl	Ph	92
1*l*	2-thienyl	Ph	90
1m	4-pyridyl	Ph	85

TABLE 2. Optimization of Reaction Conditions



entry[a]	catalyst[b]	temp (°C)	time[c] (h)	solvent	yield[d] (%)
1	none	60	30	PhMe	0
2	A	60	90	PhMe	33
3	B	60	90	PhMe	14
4	C	25	6	PhMe	trace
5	C	60	20	PhMe	70
6	C	80	3	PhMe	81
7	C	60	4	THF	75
8	C	60	1	DMF	0

[a] 0.5 mmol:0.6 mmol ratio of **1**:**2**, 1 M. [b] 4 mol % of A, tetrakis-(triphenylphosphine)palladium(0); B, dichlorobis(triphenylphosphine)palladium(II); C, bis(tri-*tert*-butylphosphine)-palladium(0). [c] To complete disappearance of **2**. [d] Isolated yield.

TABLE 3. Preparation of 3 from 1 and 2 in THF[a,b]

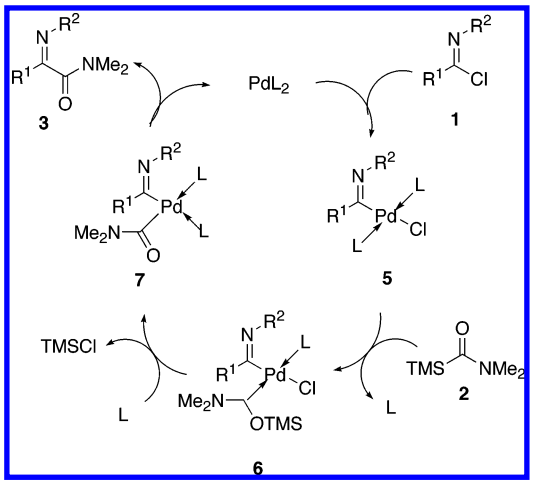
	imidoyl chloride **1**			
	R^1	R^2	time (h)	yield of **3**[c] (%)
1d	*tert*-butyl	Ph	5	95
1e	Ph	Ph	4	75 (83)[d]
1g	4-CNPh	Ph	0.8	94
1i	*tert*-butyl	CH(Me)Ph	10	77[e]
1k	2-furanyl	Ph	1	95
1*l*	2-thienyl	Ph	5	88
1m	4-pyridyl	Ph	2	93

[a] 0.5 mmol:0.6 mmol ratio of **1**:**2**, 1 M. [b] 4 mol % of bis(tri-*tert*-butylphosphine)palladium(0). [c] Isolated yield. [d] Yield from 9× scale-up. [e] 1.5 equiv of **2** used.

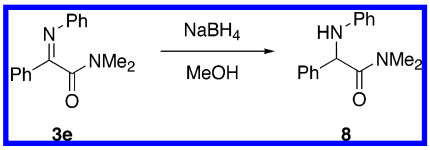
4-methoxybenzimidoyl chloride was used, total consumption of **2** was observed within 1.5 h, but subsequent chromatography only afforded 30% of *N*,*N*-dimethyl 2-(4-methoxyphenyl)-2-oxo-ethanamide (**4**), the imine hydrolysis product of the expected iminoamide.

The overall reaction may be understood by the sequence of events described in Scheme 1. Existing reports on various coupling reactions involving imidoyl chlorides and palladium catalysts suggest that the imidoylpalladium species **5** may serve as a common initial intermediate.[11,12] Following previous arguments,[13] ligand exchange between **5** and a nucleophilic carbene arising from a C → O silyl group rearrangement within **2** is postulated. Loss of TMSCl from **6** then affords **7**, which undergoes migration of the carbamoyl function and expulsion of PdL_2 to afford product **3**.[14]

SCHEME 1



To demonstrate the utility of the product α-iminoamides to afford α-aminoamides, reduction of a representative example was carried out with **3e** and sodium borohydride in methanol to give 96% of α-aminoamide **8**.



Experimental Section

Imidoyl Chlorides (Oxalyl Chloride Method). Under anhydrous conditions (Ar atmosphere), a mixture of amide (5.0 mmol) and 2,6-lutidine (8.3 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. To the stirred solution was added oxalyl chloride (5.0 mmol, 2 M solution in CH_2Cl_2 diluted with 5 mL of CH_2Cl_2) dropwise over 5 min and the reaction mixture held at 0 °C for 30 min. Solvent was evaporated under vacuum and hexane (15 mL) was added. After the solution was stirred for 1 h, solids were removed by glass frit filtration under Ar, and the filtrate was concentrated and kugelrohr distilled.

Imidoyl Chlorides (PCl_5 Method). Equimolar amounts of amide and PCl_5 were heated at 90 °C for 1 h. After the solution was cooled to 25 °C, $POCl_3$ was removed under vacuum and the residue distilled. In the preparation of **1m**, equimolar amounts of amide and PCl_5 (3.3 mmol) were refluxed in chloroform (15 mL) for 3 h. After the solution was cooled to 25 °C, 3.3 mmol of triethylamine was added and the mixture was stirred for 1 h. Solvent was removed under vacuum and diethyl ether was added. After 3 h, solids were removed by filtration and the solution evaporated. The solid product was very sensitive to manipulation.

α-Iminoamides. A Schlenk tube fitted with a fused Teflon vacuum stopcock and microstirbar was flame-heated under

(11) (a) Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1985**, *26*, 3463−3466. (b) Tanaka, M.; Kobayashi, T. *Synthesis* **1985**, 967−969.

(12) Isolation of similar complexes, prepared by a different route, has been reported: Vicente, J.; Abad, J.-A.; Martinez-Viviente, E.; Jones, P. G. *Organometallics* **2003**, *22*, 1967−1978.

(13) Cunico, R. F.; Maity, B. C. *Org. Lett.* **2003**, *5*, 4947−4949.

(14) We do not exclude the possibility that imine to carbene-carbon migration may precede TMSCl expulsion.

vacuum and refilled with Ar. Freshly prepared imidoyl chloride (0.5 mmol) and carbamoylsilane (0.6 mmol) were added and a 3-fold evacuation-Ar refill was carried out. Catalyst (4 mol % relative to imidoyl chloride) was then added, followed by dry THF or toluene (0.5 mL). The sealed reaction mixture was stirred at the indicated temperature and monitored by ^{1}H NMR, using periodic aliquots. After disappearance of starting material, volatiles were removed under vacuum and the residue was chromatographed on flash silica gel (15−25% EtOAc in hexane).

Acknowledgment. This work was supported by National Institutes of Health grant R15 GM065864.

Supporting Information Available: Analytical and spectral (IR, ^{1}H, and ^{13}C NMR) data for all imidoyl chlorides and iminoamides; details of the preparation of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050545H