Tetrahedron Letters,Vol.28,No.43,pp 5099-5102,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

A NEW SYNTHESIS OF AMIDES FROM ACYL FLUORIDES AND N-SILYLAMINES

Sundaramoorthi Rajeswari, Robert J. Jones, and Michael P. Cava

Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487-9671

Summary: Amide bonds are formed readily under mild conditions by the reaction of N-silylamines with the hydrolytically stable acyl fluorides.

In connection with the studies on the syntheses of analogs of the antitumor agent CC-1065,[1] we sought a mild procedure for the acylation of weakly basic aromatic amines using a stable and storable acyl derivative of an indole or pyrrole carboxylic acid. The acyl chorides of indole-2-carboxylic acid[2] and pyrrole-2-carboxylic acid[3] have been generated and employed only *in situ* due to their ease of hydrolysis[4] and self condensation. Acyl fluorides which are readily prepared from cyanuric fluoride[5] and carboxylic acids,[6] have been little used in synthesis due to their remarkable stability to water and other nucleophiles.[7,8] Indeed, we have observed that indole-2-carbonyl fluoride and pyrrole-2-carbonyl fluoride are, in contrast to the corresponding chlorides, stable and storable solids. We now report that fluorides like indole-2-carbonyl fluoride and pyrrole-2-carbonyl fluoride, as well as other representative acyl fluorides, react readily with both aliphatic and aromatic amines, which have been activated by N-silylation.[9] For example, indoline was silylated by N,O-bis(trimethylsilyl)acetamide (BSA) to afford the N-TMS derivative **1** which was allowed to react at room temperature - with the stable indole-2-carbonyl fluoride **2** to furnish the amide **3**.

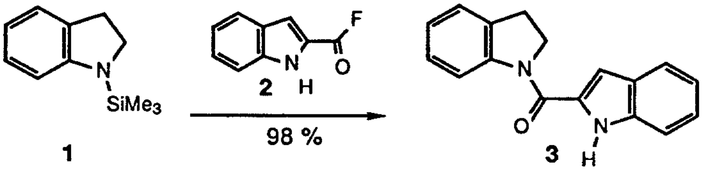

TABLE 1. Acyl Fluorides and Their Amides with N-Silylamines

Entry	Acyl fluoride	N-TMS amine	% yield of Amide
1	p-Nitrobenzoyl fluoride	Indoline	95
2	Pyrrole-2-carboxyl fluoride	Indoline	94
3	Indole-2-carboxyl fluoride	Indoline	97
4	*trans*-Cinnamoyl fluoride	Pyrrolidine	83
5	3-Acetoxybisnorcholenic acyl fluoride	Pyrrolidine	73
6	3-Acetoxybisnorcholenic acyl fluoride	Indoline	77
7	Pyridine-2,6-dicarboxyl difluoride	Indoline	78

Table 1 lists a number of acyl fluorides, which were prepared by the excellent procedure of Olah,[6] and their subsequent reaction with N-silylamines to yield the corresponding amides. To evaluate the reactivity of different types of N-silylamines, benzoyl fluoride was chosen as a standard acyl fluoride. The yields of amides (Table 2) are excellent in all cases. To get the best results from a primary amine, it was treated with exactly one half equivalent of BSA to form the N-monosilyl derivative. Addition of a catalytic amount of tetrabutylammonium fluoride dramatically increases the rate of the reaction. Table 3 compares the yield of amide **3** prepared by four different methods, and shows that our new procedure gave the best results.

TABLE 2. Reaction of Benzoyl Fluoride with N-Silylamines

Entry	Amine Used	Amide	% yield
1	Pyrrolidine	N-benzoyl pyrrolidine	90
2	Morpholine	N-benzoyl morpholine	97
3	Indoline	N-benzoyl indoline	98
4	n-Dioctylamine	N-benzoyl-n-dioctylamine	90
5	L-Proline methylester	N-benzoyl-L-proline methylester	90
6	Nornuciferine	N-benzoyl nornuciferine	93
7	Cyclohexylamine	N-benzoyl cyclohexylamine	95

TABLE 3: Preparation of 3 by Various Methods

Entry	Method employed	% yield
1	EEDQ	60
2	Acid chloride	62
3	DCC	80
4	Acid fluoride	90

Typical Procedure:

Preparation of N-Silylamines:

To indoline (357 mg, 3 mmol) in acetonitrile (5 mL) was added BSA (304.5 mg, 1.5 mmol), and the reaction mixture was stirred at room temperature under N_2 for 1h. The volatiles were removed *in vacuo*. Although no attempts were made to isolate the hydrolytically unstable N-trimethylsilyl amine, ^1H NMR data indicated its formation.

Formation of Amides from N-Silylamines:

To the N-silylamine obtained from indoline (357 mg, 3 mmol) in acetonitrile (5 mL) under N_2 was added benzoyl fluoride (372 mg, 3 mmol) and a catalytic amount of tetrabutylammonium fluoride (5 mg). After stirring for 6h at room temperature the solvent was evaporated *in vacuo.* The residue was taken up in methylene chloride and the organic layer was washed successively with a solution of $NaHCO_3$ (5%, 2 x 10 mL), 4 N HCl (2 x 10 mL), water, dried (Na_2SO_4) and evaporated to yield N-benzoyl indoline (626 mg, 98%), which was crystallized from ethyl acetate-hexane, m.p. 202°C.

References

1. For an excellent overview of this area, see: Reynolds, L. R.; McGovren, J. P.; Hurley, L. H. *J. Antibiot.* **1986**, *39*, 319. For a review of the synthetic work in this area, see: Rawal, V. H.; Jones, R. J.; Cava, M. P. *Heterocycles*, **1987**, *25*, 701.
2. Kermack, W. O.; Perkin, W. H.; Robinson, R. *J. Chem. Soc.*, **1921**, *119*, 1626.
3. Rapoport, H.; Willson, C. D. *J. Am. Chem. Soc.*, **1962**, *64*, 630.
4. Gossauer, A. *Die Chemie der Pyrrole*, **1974**, Springer Verlag, N.Y., 315.
5. Tullock C. W.; Coffman, D. D. *J. Org. Chem.*, **1961**, *25*, 2016.
6. Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis*, **1973**, 487.
7. Olah, G. A.; Kuhn, S. J. *J. Org. Chem.*, **1961**,*26*, 225.
8. Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.*, **1953**, *75*, 246.
9. N-Silylamines have been reported to react with acyl chlorides to form amides: Anderson, H. H. *J. Am. Chem. Soc.*, **1952**, *74*, 1421. Pump, J.; Wannagat, U. *Monatsch Chem.*, **1962**, *93*, 352. Bowser, J. R.; Williams, P. J.; Kurz, K. *J. Org. Chem.*, **1983**, *48*, 4111. Raucher, S.; Jones, D. S. *Synthetic Commun.*, **1985**, *15*, 1025.

Acknowledgement: This work was supported by a grant from the National Institutes of Health, CA 41995.

(Received in USA 27 July 1987)