ORGANIC LETTERS

2000
Vol. 2, No. 10
1485−1487

A General Method for Acylation of Indoles at the 3-Position with Acyl Chlorides in the Presence of Dialkylaluminum Chloride

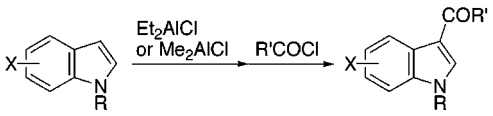
Tatsuo Okauchi,*,† Masaaki Itonaga,† Toru Minami,† Takashi Owa,‡ Kyosuke Kitoh,‡ and Hiroshi Yoshino*,‡

Department of Applied Chemistry, Kyushu Institute of Technology, 1-1, Sensuicho, Tobata, Kitakyushu, 804-8550, Japan and Tsukuba Research Laboratories, Eisai Company, Ltd., 5-1-3, Tokodai, Tsukuba, 300-2635, Japan

okauchi@che.kyutech.ac.jp

Received March 21, 2000

ABSTRACT



R=H, Me; X=H, Me, MeO, CN, CO_2Et, NO_2
R'=alkyl, alkenyl, aryl, acyl

Indoles are selectively acylated at the 3-position in high yields on treatment with a wide variety of acyl chlorides in CH_2Cl_2 in the presence of diethylaluminum chloride or dimethylaluminum chloride. The reaction proceeds under mild conditions and is applicable to indoles bearing various functional groups without NH protection.

The synthesis and reaction of indoles has been a topic of research interests for over a century because a number of their derivatives occur in nature and possess a variety of important biological activities. Since the 3-position of indole is the preferred site for electrophilic substitution and 3-acylindoles are versatile starting materials for the synthesis of a wide range of indole derivatives,[1] there are numerous methods for direct 3-acylation.[2] For the acylation of indoles, the reactions of indole salts with acyl chlorides,[3,4] Vilsmeier−Haack acylations,[5] and Friedel−Crafts acylations[6] are most widely used. The acylation of indole salts gives 3-acylindoles in good yield especially when zinc is used as a counter-cation.[4] However, it is not applicable to indoles containing

† Kyushu Institute of Technology.
‡ Eisai Company, Ltd.

(1) For some recent examples, see: (a) Fresneda, P. M.; Molina, P.; Saez, M. A. *Synlett* **1999**, 1651. (b) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053. (c) Wang, S.-F.; Chuang, C.-P. *Heterocycles* **1997**, *45*, 347. (d) Tani, M.; Matsumoto, S.; Aida, Y.; Arikawa, S.; Nakane, A.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1994**, *42*, 443.

(2) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996; p 113. (b) Pindur, U.; Pfeuffer, L.; Flo, C. *Chem.-Ztg.* **1986**, *110*, 307. (c) Engel, R. *Chem. Rev.* **1977**, *77*, 349.

(3) Davidsen, S. K.; Summers, J. B.; Albert, D. H.; Holms, J. H.; Heyman, H. R.; Magoc, T. J.; Conway, R. G.; Rhein, D. A.; Carter, G. W. *J. Med. Chem.* **1994**, *37*, 4423. (b) Macor, J. E.; Blank, D. H.; Fox, C. B.; Lebel, L. A.; Newman, M. E.; Post, R. J.; Ryan, K.; Schmidt, A. W.; Schulz, D. W.; Koe, B. K. *J. Med. Chem.* **1994**, *37*, 2509. (c) Sanchez, J. P.; Parcell, R. F. *J. Heterocycl. Chem.* **1988**, *25*, 469. (d) Bergman, J.; Venemalm, L. *Tetrahedeon Lett.* **1987**, 3741. (e) Szmuszkovicz, J. *J. Am. Chem. Soc.* **1960**, *82*, 1180.

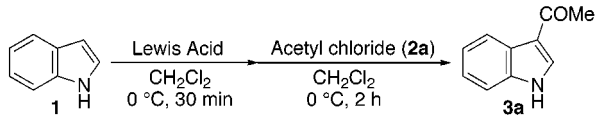
(4) Yang, C. X.; Patel, H. H.; Ku, Y.-Y.; Shah, R.; Sawick, D. *Synth. Commun.* **1997**, *27*, 2125. (b) Faul, M. M.; Winneroski, L. L. *Tetrahedron Lett.* **1997**, *37*, 4749. (c) Bergman, J.; Venemalm, L. *Tetrahedeon* **1990**, *46*, 6061.

(5) Allen, M. S.; Hamaker, L. K.; LaLoggia, A. J.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077. (b) Seemann, F.; Wiskott, E.; Niklaus, P.; Troxler, F. *Helv. Chim. Acta* **1971**, *54*, 5411. (c) Powers, J. C. *J. Org. Chem.* **1965**, *30*, 2534. (d) Anthony, W. C. *J. Org. Chem.* **1960**, *25*, 204. (e) Smith, G. F. *J. Chem. Soc.* **1954**, 3842.

(6) Nicolaou, I.; Demopoulos, V. J. *J. Heterocycl. Chem.* **1998**, *35*, 1345. (b) Nakatsuka, S.; Teranishi, K.; Goto, T. *Tetrahedron Lett.* **1994**, *35*, 2699. (c) Tani, M.; Aoki, T.; Ito, S.; Matsumoto, S.; Hideshima, M.; Fukushima, K.; Nozawa, R.; Maeda, T.; Tashiro, M.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1990**, *38*, 3261. (d) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R.; McPhail, A. T. *J. Org. Chem.* **1988**, *53*, 3170. (e) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451.

10.1021/ol005841p CCC: $19.00
Published on Web 04/27/2000

Table 1. Acetylation of **1** in the Presence of an Aluminum-Based Lewis Acid



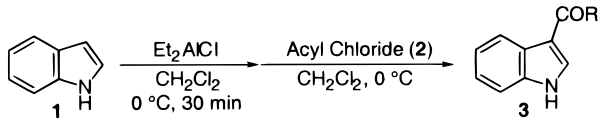
run	Lewis acid[a]	**3a**, yield/%[b]
1	Me_3Al	59
2	Et_3Al	43
3	Me_2AlCl	75
4	Et_2AlCl	86
5	$EtAlCl_2$	79
6	$AlCl_3$	—[c]
7	—[d]	—[e]

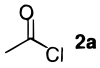
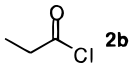
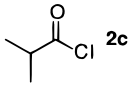
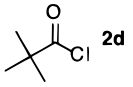
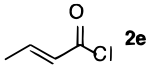
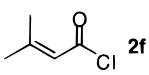
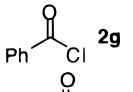
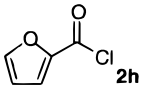
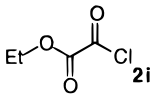
[a] 1.5 equiv of Lewis acid was used. [b] Isolated yield based on **1**. [c] 27% of **1** was recovered. [d] The reaction was carried out in the absence of Lewis acid. [e] 52% of **1** was recovered.

functional groups labile under basic or nucleophilic conditions, because Grignard reagent or alkylzinc is used for preparation of the indole salts. The Vilsmeier−Haack acylations also give good yield, but the usable amides are limited (e.g., formamide, alkylcarboxamide). The Friedel−Crafts acylations are convenient for indoles with an electron-withdrawing group, but it is indirect for other indoles since this method involves N-protection, acylation, and N-deprotection processes. We have to choose an efficient method depending of the property of the starting indole. Consequently, the need for a simple and general method for 3-acylation of both acid-sensitive and base-sensitive indoles is manifest. In our continuing investigation on synthetic antitumor agents,[7] we needed to prepare various 3-acylindole derivatives. Herein we describe a general method for acylation of indole at the 3-position using acyl chloride and alkylaluminum chloride without NH protection.

When acyl chlorides are used for the acylation of indoles, liberation of HCl is unavoidable. Since indole (**1**) is very reactive to protic acid, relatively neutral conditions are required to obtain 3-acylindole in good yield. To scavenge the acid, the acylation of **1** with acetyl chloride (**2a**) was carried out in the presence of alkylaluminum. As shown in Table 1, the acylation proceeded cleanly to give 3-acylindole

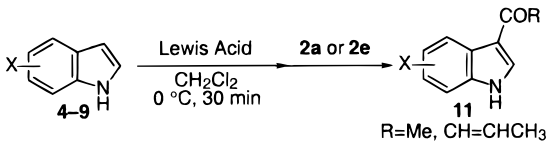
Table 2. Acylation of **1** with Several Acyl Chlorides **2**

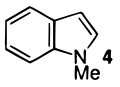
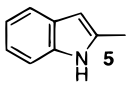
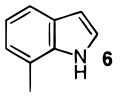
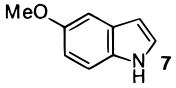
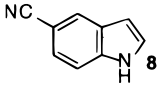
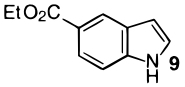
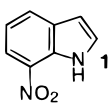


run	acyl chloride[a]	time/h	**3**, yield/%[b]
1	 **2a**	2	86
2	 **2b**	1.5	81
3	 **2c**	1.5	84
4	 **2d**	2	87
5	 **2e**	2	79
6	 **2f**	3	89
7	 **2g**	2	80
8	 **2h**	72	91
9	 **2i**	3	72

[a] 2 equiv of acyl chloride was used. [b] Isolated yield based on **1**.

Table 3. Acylation of Substituted Indoles **4**−**9** with **2a** and **2e**



run	indole	acyl chloride[a]	Lewis acid[b]	conditions	**11**, yield/%[c]
1	 **4**	**2a**	Et_2AlCl	0 °C, 3 h	85
2		**2e**	Et_2AlCl	0 °C, 3 h	70
3	 **5**	**2a**	Et_2AlCl	0 °C, 3 h	89
4		**2e**	Et_2AlCl	0 °C, 2 h	80
5	 **6**	**2a**	Et_2AlCl	0 °C, 2 h	80
6		**2e**	Et_2AlCl	0 °C, 3 h	91
7	 **7**	**2a**	Et_2AlCl	0 °C, 4 h	89
8		**2e**	Et_2AlCl	0 °C, 4 h	71
9	 **8**	**2a**	Et_2AlCl	rt, 3 h	72
10		**2e**	Et_2AlCl	rt, 4 h	75
11	 **9**	**2a**	Et_2AlCl	0 °C, 3 h	91
12		**2e**	Et_2AlCl	0 °C, 12 h	64
13	 **10**	**2a**	Et_2AlCl	0 °C, 2 h	—[d]
14		**2a**	Me_2AlCl[e]	0 °C, 4 h	quant
15		**2e**	Me_2AlCl[e]	0 °C, 2 h	quant

[a] 1.5 equiv of acyl chloride was used. [b] 1.5 equiv of Lewis acid was used unless otherwise indicated. [c] Isolated yield. [d] Complex mixture. [e] 2.5 equiv of Me_2AlCl was used.

3a without any byproducts resulting from acid-catalyzed decomposition of **1** (runs 1−5). Note that the acylation at the 3-position proceeded regioselectively without NH protection. The highest yield was obtained when Et_2AlCl was used (run 4). The reactions using Et_3Al and Me_3Al (runs 1, 2) led to lower yields, probably because a nucleophilic attack of the alkyl group on aluminum to acetyl chloride occurred competitively. As expected, the use of $AlCl_3$ resulted in decomposition and undesirable oligomerization of indole due to strong Lewis acidity of $AlCl_3$ and liberated HCl (run 6).

Next, we examined the reaction of several acyl chloride **2b**−**i** with indole (**1**) in the presence of Et_2AlCl. As summarized in Table 2, linear or branched aliphatic acyl chlorides, **2b**−**d**, α,β-unsaturated acyl chlorides, **2e,f**, an aromatic acyl chlorides, **2g**,**h**, and ethyl chlorooxoacetate (**2i**) smoothly reacted with **1** in the presence of Et_2AlCl to afford the expected 3-acylindoles **3b**−**i** in high yields. Instead of acid chlorides, acid anhydrides gave **3** in poor yields, along with several byproducts.

Having developed a convenient method for 3-acylation of indole,[8] we became interested in exploring the reactions of acyl chlorides **2a,e** with indoles other than **1** to see if the acylation could proceed in the same fashion. As shown in Table 3, *N*-alkylated indole **4** and indoles with an electron-donating group or an electron-withdrawing group **5**−**9** reacted with **2a,e** producing substituted 3-acylindoles **11** in high yields, while 7-nitroindole (**9**) gave a complex mixture in the presence of Et_2AlCl. Interestingly, the use of Me_2AlCl instead of Et_2AlCl in this reaction afforded desired 3-acylindoles in quantitative yields. Both acid-sensitive, **4**−**7**, and base-sensitive, **8** and **9**, indoles were tolerated under these acylation conditions.

In conclusion, we have developed a general method for acylation of indoles at the 3-position with a wide variety of acyl chlorides in the presence of Et_2AlCl or Me_2AlCl. This 3-acylation proceeds under mild conditions and is applicable to indoles bearing various functional groups without NH protection. The simple procedure, mild reaction conditions, and generality render this method a valuable addition to indole chemistry.

Acknowledgment. We thank the Center for Instrumental Analysis KIT for the measurement of analytical data. We also thank the staff of Eisai Analytical Chemistry Section for the measurement of analytical data.

OL005841P

(7) Yoshino, H.; Ueda, N.; Niijima, J.; Sugumi, H.; Kotake, Y.; Koyanagi, N.; Yoshimatsu, K.; Asada, M.; Watanabe, T.; Nagasu, T.; Tsukahara, K.; Iijima, A.; Kitoh, K. *J. Med. Chem.* **1992**, *35*, 2496. (b) Owa, T.; Yoshino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. *J. Med. Chem.* **1999**, *42*, 3789.

(8) **Representative Experimental Procedure of Acylation of Indole at the 3-Position.** To a CH_2Cl_2 solution (2 mL) of indole (**1**) (54 mg, 0.46 mmol) was added 0.71 mL (0.70 mol) of Et_2AlCl (0.98 mol/L in hexane) at 0 °C. The mixture was stirred at 0 °C for 30 min. To this solution was added dropwise a CH_2Cl_2 solution (2 mL) of acetyl chloride (**2a**) (54 mg, 0.69 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2 h, and pH 7 aqueous buffer was added to quench the reaction. After usual workup, the crude product was purified by TLC on silica gel to give 3-acetylindole (**3a**) (63 mg, 86% yield).