JOC Notes

Regiospecific *C*-Acylation of Pyrroles and Indoles Using *N*-Acylbenzotriazoles

Alan R. Katritzky,* Kazuyuki Suzuki, Sandeep K. Singh, and Hai-Ying He§

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

katritzky@chem.ufl.edu

Received February 11, 2003

Abstract: Reactions of pyrrole (**2**) or 1-methylpyrrole (**4**) with readily available *N*-acylbenzotriazoles **1a**−**g** (RCOBt, where R = 4-tolyl, 4-nitrophenyl, 4-diethylaminophenyl, 2-furyl, 2-pyridyl, 2-indolyl, or 2-pyrrolyl) in the presence of $TiCl_4$ produced 2-acylpyrroles **3a**−**g** and **5a**−**g** in good to excellent yields. 1-Triisopropylsilylpyrrole (**6**) under the same conditions gave the respective 3-acylpyrroles **7a**−**g**. Similarly, indole (**9**) and 1-methylindole (**11**) gave the corresponding 3-acylated derivatives **10a**−**g** and **12a**−**g**. These results demonstrate that *N*-acylbenzotriazoles such as **1c**,**f**,**g** are mild, regioselective, and regiospecific C-acylating agents of particular utility when the corresponding acid chlorides are not readily available.

The synthesis and reactions of acylpyrroles and acylindoles have received continued attention. Acylpyrroles are intermediates in the multistep synthesis of chemotherapeutic agents, occur in nature, and possess medicinal value.[1,2] Acylindoles are precursors to a variety of biologically important alkaloids.[3]

General methods for the introduction of an acyl substituent at C-2 of pyrroles include reactions with acid chlorides, Vilsmeier−Haack reagents,[4a,b] seleno-esters,[5a] thiol-esters[5b] nitrilium salts,[6a,b] and the use of α-(dimethylamino)-α-pyrrolylacetonitrile[7] or pyrrylmagnesium halide[8] precursors. Similar synthesis of 3-acylpyrroles requires the presence of sterically or electronically effective directing substituents on the nitrogen atom.[9]

The most common methods for the preparation of 3-acylindoles include Friedel−Crafts[10a,b] or Vilsmeier−Haack[11a,b] acylations; use of nitrilium,[6,12a,b] dialkoxy carbenium,[13] or *N*-(α-haloacyl)- pyridinium[14] salts; and the acylation of indole magnesium[15a,b] or zinc[16a,b] reagents.

However, there are limitations associated with the literature methods: selective direct Friedel−Crafts acylations of electron-rich heterocycles can require the presence of an electron-withdrawing substituent, diacylation may occur, or mixtures of isomers may be obtained.[11a,17−19] Some heterocycles are sensitive to acids such as HCl. Vilsmeier−Haack acylations are mostly limited to formamide and alkylcarboxamides.[11b]

N-Acylbenzotriazoles have been previously reported by us as mild neutral N-acylating agents for the preparation of primary, secondary, and tertiary amides[20a] and specifically for formylation[20b] and trifluoroacylation.[20c] We have also used *N*-acylbenzotriazoles for the O-acylation of aldehydes[20d] and for regioselective C-acylation of ketone enolates into *β*-diketones.[20e] We now apply *N*-acylbenzotriazoles for mild regioselective and regiospecific C-acylations of pyrroles and indoles, including preparations of several acyl-pyrroles and -indoles not easily available by known methods.

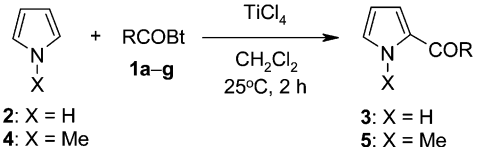
Preparation of *N*-Acylbenzotriazoles. The present work concentrated on (i) previously less studied arylcarbonyl or heterocyclocarbonyl examples as compared to the more common alkylcarbonyl derivatives and (ii) cases where the corresponding acyl chlorides are unstable or inconvenient to prepare, for example, 4-diethylaminoben-

§ New address: ImClone Systems Incorporated, 180 Varick St., New York, NY 10014

(1) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: New York, 1996; Vol. 2, p 207.
(2) Massa, S.; Di Santo, R.; Artico, M. *J. Heterocycl. Chem.* **1990**, *27*, 1131.
(3) Gribble, G. W. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Sainsbury, M., Ed.; Elsevier: Amsterdam, 1997; p 69.
(4) (a) Jones, R. A.; Bean, G. P. In *The Chemistry of Pyrroles*; Academic Press: New York, 1977; p 151. (b) Candy, C. F.; Jones, R. A.; Wright, P. H. *J. Chem. Soc. C* **1970**, 2563. (c) White, J.; McGillivray, G. *J. Org. Chem.* **1977**, *42*, 4248.
(5) (a) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860. (b) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647.
(6) (a) Eyley, S. C.; Giles, R. G.; Heaney, H. *Tetrahedron Lett.* **1985**, *26*, 4649. (b) Black, D. St. C. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: New York, 1996; Vol. 2, p 44.
(7) Bray, B. L.; Muchowski, J. M. *J. Org. Chem.* **1988**, *53*, 6115.
(8) Patterson, J. M. *Synthesis* **1976**, 281.
(9) (a) Simchen, G.; Majchrzak, M. W. *Tetrahedron Lett.* **1985**, *26*, 5035. (b) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317. (c) Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896.
(10) (a) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451. (b) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485.
(11) (a) Sundberg, R. J. In *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Remers, W. A.; Brown, R. K. In *The Chemistry of Heterocyclic Compounds*; Houlihan, W. J., Ed.; John Wiley: New York, 1972; Vol. 25, p 116.
(12) (a) Allen, M. S.; Hamaker, L. K.; La Loggia, A. J.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077. (b) Powers, J. C. *J. Org. Chem.* **1965**, *30*, 2534.
(13) Pindur, U.; Flo, C.; Akgun, E.; Tunali, M. *Liebigs Ann. Chem.* **1986**, 1621.
(14) Bergman, J.; Backvall, J.-E.; Lindstrom, J.-O. *Tetrahedron* **1973**, *29*, 971.
(15) (a) Heacock, R. A.; Kasparek, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1969; p 43. (b) Bergman, J.; Venemalm, L. *Tetrahedron Lett.* **1987**, *28*, 3741.
(16) (a) Yang, C.; Patel, H. H.; Ku, Y.-Y.; Shah, R.; Sawick, D. *Synth. Commun.* **1997**, *27*, 2125. (b) Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061.
(17) Belanger, P. *Tetrahedron Lett.* **1979**, 2505.
(18) Harsanyi, M. C.; Norris, R. K. *J. Org. Chem.* **1987**, *52*, 2209.
(19) Carson, J. R.; Davis, N. M. *J. Org. Chem.* **1981**, *46*, 839.
(20) (a) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210. (b) Katritzky, A. R.; Chang, H.-X.; Yang, B. *Synthesis* **1995**, 503. (c) Katritzky, A. R.; Yang, B.; Semenzin, D. *J. Org. Chem.* **1997**, *62*, 726. (d) Katritzky, A. R.; Pastor, A.; Voronkov, M. V. *J. Heterocycl. Chem.* **1999**, *36*, 777. (e) Katritzky, A. R.; Pastor, A. *J. Org. Chem.* **2000**, *65*, 3679.

10.1021/jo034187z CCC: $25.00 © 2003 American Chemical Society
Published on Web 06/07/2003

TABLE 1. 2-Acylation of Pyrrole (2) and 1-Methylpyrrole (4) Using *N*-Acylbenzotriazoles 1a−g



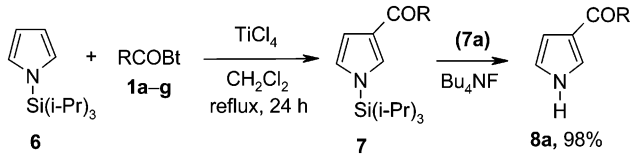
				previous work		
entry	reactants	R	product (yield %)	reagent	yield[a] %	ref
1	**2** + **1a**	4-$CH_3C_6H_4$	**3a** (87)	4-$CH_3C_6H_4COA$[b]/$POCl_3$	86	4c
2	**2** + **1b**	4-$NO_2C_6H_4$	**3b** (60)	4-$CH_3C_6H_4COA$[b]/$POCl_3$	91	4c
3	**2** + **1c**	4-$Et_2NC_6H_4$	**3c** (21)			
4	**2** + **1d**	2-furyl	**3d** (91)	thiolester/Grignard method[c]	90	5b
5	**2** + **1e**	2-pyridyl	**3e** (47)	2-pyridylCOCl/$AlCl_3$	62	24
6	**2** + **1f**	2-indolyl	**3f** (39)			
7	**2** + **1g**	2-pyrrolyl	**3g** (47)	2,2′-dipyrrylthioketone/KOH/H_2O_2	76	25
8	**4** + **1a**	4-$CH_3C_6H_4$	**5a** (90)	4-$CH_3C_6H_4COA$[d]/$POCl_3$	65	26
9	**4** + **1b**	4-$NO_2C_6H_4$	**5b** (74)	4-$NO_2C_6H_4COCl$[e]	73	27
10	**4** + **1c**	4-$Et_2NC_6H_4$	**5c** (51)			
11	**4** + **1d**	2-furyl	**5d** (94)	acylation of furan[f]	76	28
12	**4** + **1e**	2-pyridyl	**5e** (54)	2-pyridylCOCl·HCl/3 N NaOH	34	29
13	**4** + **1f**	2-indolyl	**5f** (51)			
14	**4** + **1g**	2-pyrrolyl	**5g** (75)			

[a] Isolated yield. [b] A = morpholide (freshly prepared from acid chloride and an equimolar mixture of morpholine and triethylamine), 20 h, 25 °C. [c] 2-Furoyl-S-2-pyridyl, MeMgCl. [d] A = morpholide, 45 h, 25 °C. [e] Refluxing in toluene for 18 h. [f] *N*-Methyl-2-pyrrolylCOOH, $(CF_3CO)_2O$, phosphonic resin.

zoyl, indolyl-3-carboxyl, or pyrrolyl-2-carboxyl derivatives. The starting *N*-acylbenzotriazoles **1a**−**g** with aryl or heterocyclic groups (R = 4-tolyl, 4-nitrophenyl, 4-diethylaminophenyl, 2-furyl, 2-pyridyl, 2-indolyl, or 2-pyrrolyl) were prepared from the corresponding carboxylic acids by treatment with 1-(methylsulfonyl)benzotriazole following the previously reported one-step general procedure.[20e]

Preparation of 2-Acylpyrroles. Regioselectivity in the acylation of pyrroles is a function of the Lewis acid,[21] reaction solvent,[22] and the acylating agent.[4a] Accordingly, we studied the effect of these parameters to optimize the reaction conditions. Our initial results in the acylation of pyrrole using 1*H*-1,2,3-benzotriazolyl(4-methylphenyl)-methanone (**1a**) in the presence of $ZnBr_2$ as the Lewis acid in dichloroethane gave low regioselectivity: a 3:1 ratio of 2- and 3-isomers (4-methylphenyl)(1*H*-pyrrol-2-yl)methanone and (4-methylphenyl)(1*H*-pyrrol-3-yl)methanone, respectively, was detected in the reaction mixture after 3 h (^{1}H NMR analysis of an aliquot). This ratio changed to 5:1 on continuing the reaction for 12 h, and 2- and 3-isomers were obtained in a combined yield of 75%. No diacylation products were formed under these reaction conditions. Formation of mixtures of 2- and 3-isomers in the acylation of pyrroles and the interconversion of the isomers has been observed previously.[19] The use of $TiCl_4$ as the Lewis acid proved to be beneficial: the acylation of pyrrole using 1*H*-1,2,3-benzotriazolyl(4-methylphenyl)methanone (**1a**) in dichloromethane produced regiospecifically the 2-isomer, (4-methylphenyl)-(1*H*-pyrrol-2-yl)methanone (**3a**), in 87% yield in a short reaction time of 2 h. No formation of the 3-isomer was detected in the crude reaction mixture by ^{1}H NMR. Thus,

TABLE 2. 3-Acylation of TIPS−Pyrrole (6) Using *N*-Acylbenzotriazoles 1a−g



entry	reactants	R	product (yield %)[a]
1	**6** + **1a**	4-$CH_3C_6H_4$	**7a** (92)
2	**6** + **1b**	4-$NO_2C_6H_4$	**7b** (72)
3	**6** + **1c**	4-$Et_2NC_6H_4$	**7c** (90)
4	**6** + **1d**	2-furyl	**7d** (89)
5	**6** + **1e**	2-pyridyl	**7e** (54)
6	**6** + **1f**	2-indolyl	**7f**[b]
7	**6** + **1g**	2-pyrrolyl	**7g** (78)

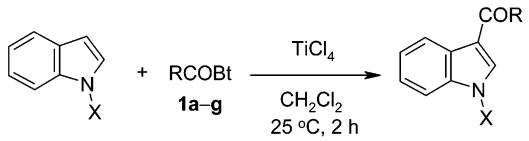
[a] Isolated yield. [b] Could not be isolated in a pure form.

a set of appropriate reaction conditions was developed for the regiospecific 2-acylation of pyrroles using *N*-acylbenzotriazoles.

The above optimized reaction conditions were used for the synthesis of a variety of 2-acylpyrroles. Reactions of unsubstituted pyrrole (**2**) with *N*-acylbenzotriazoles **1b**−**g** gave 2-acylpyrroles **3b**−**g** in 21−91% yields. Similar results were obtained when *N*-methylpyrrole (**4**) was acylated under these reaction conditions: the corresponding 2-acylated *N*-methylpyrroles **5a**−**g** were produced in 51−94% yields. Again, no formation of the 3-isomer was detected in the crude reaction mixtures. Structures **3a**−**g** and **5a**−**g** are supported by their ^{1}H and ^{13}C NMR spectra and microanalysis or HRMS data. These results illustrate the general applicability of this method for the preparation of 2-acylpyrroles under mild conditions (25 °C) and short reaction times (2 h). In comparison, literature procedures for the known compounds usually involve at least one of the following: (i)

(21) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.
(22) Ottoni, O.; Neder, A. de V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005.

TABLE 3. 3-Acylation of Indole (9) and 1-Methylindole (11) Using *N*-Acylbenzotriazoles 1a−g



9: X = H
11: X = Me

10: X = H
12: X = Me

				previous work		
entry	reactants	R	product (yield %)[a]	reagent	yield[a] %	ref
1	**9** + **1a**	4-$CH_3C_6H_4$	**10a** (92)	EtMgI/4-$CH_3C_6H_4COCl$	65	30
2	**9** + **1b**	4-$NO_2C_6H_4$	**10b** (66)	4-$NO_2C_6H_4COCl/AlCl_3$	34	31
3	**9** + **1c**	4-$Et_2NC_6H_4$	**10c** (66)			
4	**9** + **1d**	2-furyl	**10d** (64)	2-furylCOCl/Et_2AlCl	91	10b
5	**9** + **1e**	2-pyridyl	**10e** (73)	indirect method[b]	48	32
6	**9** + **1f**	2-indolyl	**10f** (86)	indirect method[c]		33
7	**9** + **1g**	2-pyrrolyl	**10g** (15)			
8	**11** + **1a**	4-$CH_3C_6H_4$	**12a** (92)	4-$CH_3C_6H_4COCl/AlCl_3$	40	34
9	**11** + **1b**	4-$NO_2C_6H_4$	**12b** (74)			
10	**11** + **1c**	4-$Et_2NC_6H_4$	**12c** (79)			
11	**11** + **1d**	2-furyl	**12d** (90)			
12	**11** + **1e**	2-pyridyl	**12e** (70)			
13	**11** + **1f**	2-indolyl	**12f** (27)			
14	**11** + **1g**	2-pyrrolyl	**12g** (48)			

[a] Isolated yield. [b] DDQ oxidation of 3-(2-pyridylmethyl)-indole. [c] From bis(*N*-phenylsulfonylindol-2-yl) derivative.

requirement of the preparation of morpholides prior to acylation, (ii) low regioselectivity, or (iii) requirement of long reaction times (25−45 h) (Table 1).[4c,26]

Preparation of 3-Acylpyrroles. Regioselective synthesis of 3-acyl-1*H*-pyrroles have until recently been time-consuming and problematic, requiring indirect methods.[23] The most effective device has been the use of a bulky group on the nitrogen atom: *tert*-butyldimethylsilyl (TBDMS)[9a] and especially triisopropylsilyl (TIPS)[9b] groups allow easy 3-acylation of pyrroles as sterically effective, stable, and easily cleavable N-substituents. Accordingly, following Tidwell and Muchowski, we have utilized the *N*-triisopropylsilyl substituent for the preparation of 3-acylpyrroles using *N*-acylbenzotriazoles as the acylating agents. Thus, TIPS-pyrrole (**6**) was prepared from the sodium salt of pyrrole and triisopropylsilyl chloride in 90% yield.[9b] Reaction of **6** with *N*-acylbenzotriazoles **1a**−**g** in the presence of $TiCl_4$ produced exclusively the corresponding 3-acylated *N*-triisopropylsilylpyrroles **7a**−**g** in 54−92% yields, except **7f**, which could not be isolated in a pure form. 3-Acylated *N*-triisopropylsilylpyrroles **7a**−**e** and **7g** are all novel compounds and have been fully characterized by ^1H and ^{13}C NMR spectroscopy and elemental analysis or high-resolution mass spectrometry (Table 2). Fluoride ion-induced desilylation[9b] of 3-acylated *N*-triisopropylsilylpyrrole **7a** occurred readily at room temperature to give (4-methylphenyl)(1*H*-pyrrol-3-yl)-methanone (**8a**) in 98% yield.

Preparation of 3-Acylindoles. The method developed above for the 2-acylation of pyrroles and *N*-methylpyrroles was applied to the acylation of unsubstituted indole (**9**). 3-Acylindoles **10a**−**g** were obtained exclusively and in good yields in reactions of indole (**9**) with *N*-acylbenzotriazoles **1a**−**g** in the presence of $TiCl_4$. Similarly, reactions of *N*-methylindole (**11**) gave the corresponding acylated *N*-methylindoles **12a**−**g** in 27−92% yields (Table 3). Novel 3-acylated indoles were characterized by their ^1H and ^{13}C NMR spectra and elemental analysis. The previously observed complications in the acylation of unsubstituted indole such as simultaneous formation of 1-acylated and/or 1,3-diacylated products were absent.[11a,b] Our method also removes the possibility of decomposition or self-polymerization of indole commonly observed due to the release of HCl when acyl chlorides are employed.[22]

In summary, we have introduced a convenient and general method for direct access to isomerically pure 2-acylpyrroles, 3-acylpyrroles, or 3-acylindoles under mild reaction conditions using readily available *N*-acylbenzotriazoles. Use of *N*-acylbenzotriazoles **1c**,**f**,**g** illustrates the preparation of acyl derivatives not easily available by other methods.

(23) Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353.
(24) Rao, K. V.; Reddy, G. C. *J. Agric. Food Chem.* **1990**, *38*, 1260.
(25) Shi, D.-F.; Wheelhouse, R. T.; Sun, D.; Hurley, L. H. *J. Med. Chem.* **2001**, *44*, 4509.
(26) Artico, M.; Corelli, F.; Massa, S.; Stefancich, G. *J. Heterocycl. Chem.* **1982**, *19*, 1493.
(27) Carmosin, R. J.; Carson, J. R.; Pitis, P. U.S. Pat. 5418236, 1995; *Chem. Abstr.* **1995**, *123*, 286086.
(28) Fayed, S.; Delmas, M.; Gaset, A. *Synth. Commun.* **1982**, *12*, 1121.
(29) Carson, J. R.; Pitis, P. M. PCT Int. Appl. 0202521, 2002; *Chem. Abstr.* **2002**, *136*, 102279.
(30) N. V. Koninklijke Pharmaceutische Fabrieken voorheen Brocades-Stheeman & Pharmacia Belg. Pat. 637352, 1964; *Chem. Abstr.* **1965**, *62*, 10415b.
(31) Sawada, K.; Okada, S.; Kuroda, A.; Watanabe, S.; Sawada, Y.; Tanaka, H. *Chem. Pharm. Bull.* **2001**, *49*, 799.
(32) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.
(33) Mahboobi, S.; Kuhr, S.; Pongratz, H.; Popp, A.; Hufsky, H.; Bohmer, F.; Teller, S.; Uecker, A.; Beckers, T. U.S. Pat. 6407102, 2002; *Chem. Abstr.* **2002**, *131*, 336939.
(34) Wang, S.-F.; Chuang, C.-P. *Heterocycles* **1997**, *45*, 347.
(35) Katritzky, A. R.; Shobana, N.; Pernak, J.; Afridi, A. S.; Fan, W.-Q. *Tetrahedron* **1992**, *48*, 7817.
(36) Nicolaou, I.; Demopoulos, V. J. *J. Heterocycl. Chem.* **1998**, *35*, 1345.

Experimental Section

Melting points are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal references) unless specified otherwise.

General Procedure for C-Acylation of Pyrroles (2, 4, 6) or Indoles (9, 11) Using *N*-Acylbenzotriazoles 1a−g. To a mixture of pyrrole (**2**, **4**, **6**) or indole (**9**, **11**) (2.5 mmol) and *N*-acylbenzotriazole (2.0 mmol) in CH_2Cl_2 (15 mL) was added $TiCl_4$ (1.0 M in CH_2Cl_2, 4 mL, 4 mmol), and the mixture was stirred for a specified time and temperature (see Tables **1**−**3** for details). The reaction was quenched by adding MeOH (2 mL). The solvents were evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel using hexanes/ethyl acetate (2:1) as the eluent to give the C-acylated pyrroles **3a**−**g**, **5a**−**g**, and **7a**−**g** or indoles **10a**−**g** and **12a**−**g** in pure form.

Supporting Information Available: Characterization data and general procedure for the preparation of *N*-acylbenzotriazoles **1a**−**g**, characterization data for compounds **3a**−**g**, **5a**−**g**, **7a**−**g**, **8a**, **10a**−**g**, and **12a**−**g**, and ^{1}H and ^{13}C NMR spectra of compound **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034187Z