Reaction-Pathways and Synthetic Applications of 3-Indolyl-methyl-ethoxycarbenium Tetrafluoroborates**

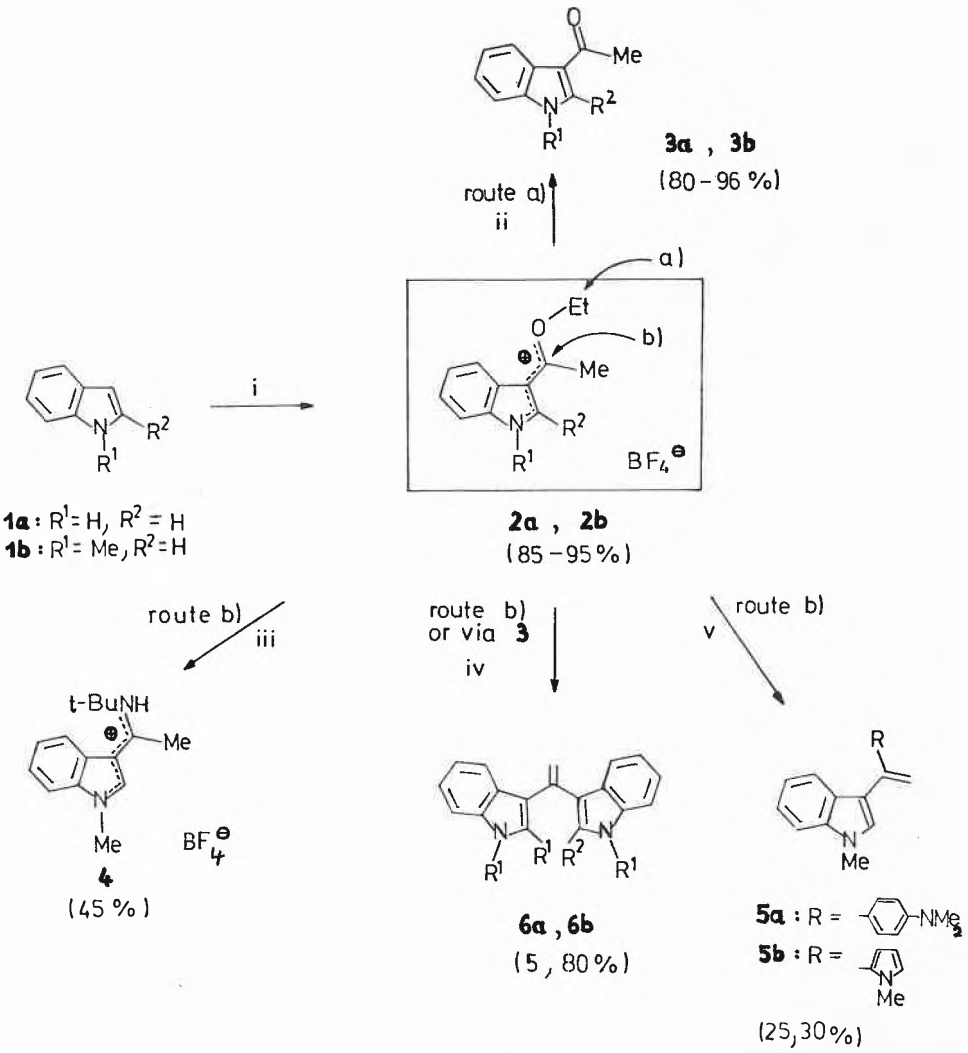
Ludwig Pfeuffer, Johann Müller, and Ulf Pindur*

Abstract: The 3-unsubstituted indoles **1a**, **1b**, and **1c** react with triethyl orthoacetate in dichloromethane by means of proton catalysis to form the stable 3-indolyl-methyl-ethoxycarbenium tetrafluoroborates **2a**, **2b**, and **2c**, respectively. The cationic species represent key compounds for interesting subsequent reactions including further functionalization of the indole skeleton.

Regioselective acylations of the indole nucleus continues to command most attention in synthon chemistry concerned with deriving indole alkaloids and pharmacologically active compounds[1–3]. After a critical perusal of the literature[4] it seems to us that the search for further acylation processes, especially mild ones and regioselective ones, is well worth pursuing. In the present communication we now describe the acetylation of some indoles with triethyl orthoacetate, and we discuss some synthetically useful reaction paths of key compounds, viz. 3-indolyl-methyl-ethoxycarbenium ions **2** (Scheme 1).

The reactive (3-unsubstituted) indoles **1a**, **1b**, and **1c** react almost quantitatively with triethyl orthoacetate, when HBF_4-ether is added as catalyst, in dichloromethane to form the stable carbenium tetrafluoroborates **2a**, **2b**, and **2c**. The cations possess «ambidental» electrophilic reactivity[5] and should thus be adapted to trigger subsequent reactions along two separate paths (Scheme 1, route *a* and route *b*). The direction preferred is kinetically or thermodynamically controlled first of all by the conditions under which the reaction takes place and by the nature of the nucleophilic partner. A nucleophilic solvent (e.g. methanol) dealkylates **2** smoothly in a peripheral reaction, producing the 3-acetylindoles **3** in excellent yield (Schemes 1, 2; route *a*). This reaction sequence is particularly favoured in the case of highly stabilized alkoxycarbenium ions, the cations **2** being a particularly good case in point. This mild procedure, which can also be carried out in situ, without isolating the cations **2**, makes it possible to derive simply, highly regioselectively, and almost quantitatively the acetylated indoles **3**. Acetylation in the case of C-3-unsubstituted indoles is indeed possible with other acetylation equivalents too, e.g. acetic anhydride[6–8] acetyl chloride[7], 2-methyl-4,5-dihydroimidazole/Ac_2O[9], 2-methyl-4,5-dihydrooxazole/Ac_2O [10], or Vilsmeier-Haack reagent[11]. However, in the Ac_2O medium, when use is made of indoles which are unsubstituted at N-1, a competing *N*-acetylation can occur.

Acetyl chloride as a reagent leads, furthermore, by way of the 3-acetylindole step, to the formation of indolenine dyes[7, 12, 13] which generally are responsible for surface colouration in acetylated in-



Scheme 1. Reagents and conditions: *i*: $MeC(OEt)_3$, $HBF_4 \cdot Et_2O$, CH_2Cl_2, 1 h, 20 °C; *ii*: MeOH, 1 h, 20 °C; *iii*: $tBuNH_2$, CH_2Cl_2, 3 h, 20 °C; *iv*: **1a** or **1b**, CH_2Cl_2 or $MeCO_2Et$ or MeOH, 2 h, 20 °C; *v*: **2a**, *N*,*N*-dimethylaminobenzene or *N*-methylpyrrole, $EtNO_2$, 12 h, 70 °C. Compounds **2–5** gave satisfactory elemental analyses and NMR-, IR-, and mass spectra.

* *Correspondence:* Prof. Dr. U. Pindur
Department of Pharmacy and Food Chemistry
Würzburg University
Am Hubland, D-8700 Würzburg
(Federal Republic of Germany)

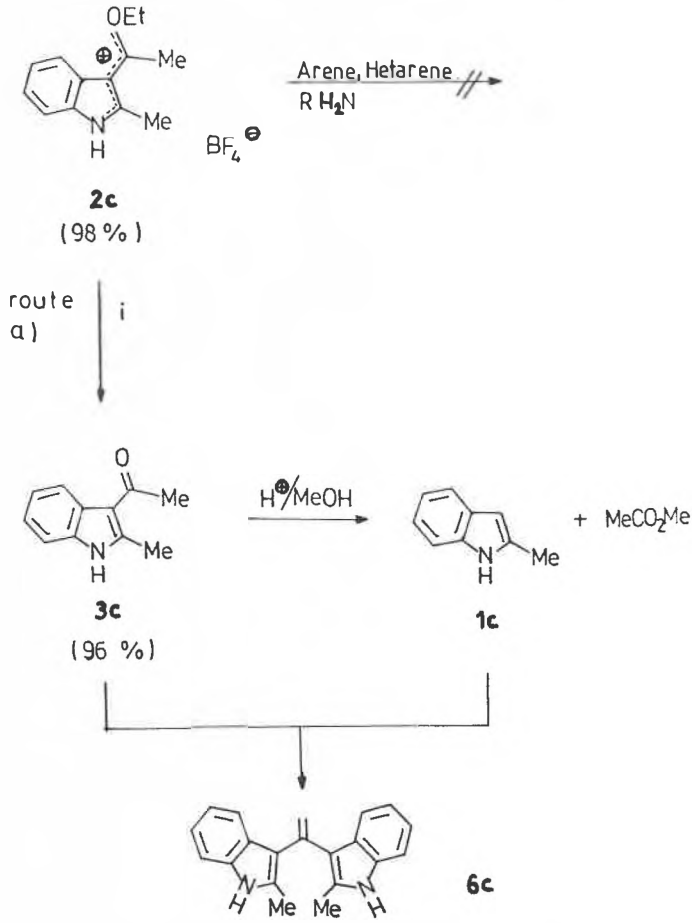
** Reactions of Electron-Rich Heterocycles with Derivatives of Carboxylic Ortho Acids, Part 6. – Part 5: See [1].

doles. Our method, then, had to be superior to the acetylation of indoles with Ac_2O or AcOCl. It should also provide a valuable addition, from the point of view of synthesizing, to the newer procedures which make use of 5-ring heterocycles as acetylation equivalents[9, 10]. However, the great advantage of our present reaction is the simplicity of the procedure, with its high degree of regioselectivity, its short reaction time and mild conditions under which it works.

The electrophilic reagent **2** is ambidentally reactive and therefore nucleophilic substitution reactions should also be possible at the carbenium centre (Scheme 1, route *b*). In fact, The *N*-protected cation **2b** reacts smoothly in a kinetically controlled way with primary amines, e.g. *tert*-butylamine, to form the benzoanellated trimethine dye **4.** If the highly nucleophilic starting compounds **1a** or **1b** are offered as reaction partners to **2a** or **2b**, then the reaction produces the 3,3'-bisindolylethenes **6a** and **6b** (Scheme 1)[13]. When dichloromethane or ethyl acetate are the solvent used, this sequence takes the form of a direct addition and (ethanol) elimination reaction. When pure methanol is used, however, this condensation leads to the formation of **6a** or **6b** by way of **3a** or **3b**, which should in this case be regarded as intermediates. In both of these reactions the protons released exhibit an autocatalytic effect which on the whole results in an acceleration of the rate of reaction.

The cations **2a** and **2b**, as also the synthetically equivalent acetylindoles **3a** and **3b**, are also useful building blocks for the derivation of 1(3-indolyl)-1-phenyl(or heteroaryl)-ethenes **5**[14]. These compounds as 3-vinylindole equivalents are potential precursors for the formation of selectively functionalized carbazoles[14]. We used the highly nucleophilic reagents *N*,*N*-dimethylaminobenzene and *N*-methylpyrrole and **2b** as a model synthesis and in this way established an example of this reaction step, which is certainly capable of further experimental application. Access to the 3-vinylindoles **5a** and **5b** is by way of relatively simple reaction with yields of 25 and 30%. Extending the synthetic potential to analogues of **5** is currently under investigation.

The cation **2c** is a N-vinylogous (ethoxy)aminocarbenium ion which is highly stabilized by double hyperconjugation. In terms of route *b* its reactivity is somewhat anomalous. As a result of its higher thermodynamic stability, compared to **2a** or **2b**, no significant direct reaction at the carbenium centre takes place with electron-rich arenes, heteroarenes or primary amines (Scheme 2). The cation **2c** merely reacts in a peripheral way as a good alkylation reagent (route *a*)[5]. Here a reaction sequence typical of **2c** is described. In methanol, a S_N2-type dealkylation sets in spontaneously, forming **3c**. This, being a vinylogous acetamide, is to some extent subject to proton catalyzed methanolytic cleavage to **1c** under mild reflux condition. After a reaction lasting approximately 1–2 h it is possible to isolate both the 3-acetylindole **3c** and also the condensation product **6c**[13, 15] formed from **3c** and the reactive indole **1c**. In order to derive also unsymmetrical bisindolylethenes of type **6** from **2c** we offered the indoles **1a** or **1b** to the cation **2c** as a nucleophilic reaction partner in methanol. An analysis of the product of this reaction, however, documents the fact that the main product of this competing reaction remains undoubtedly the ethene **6c**. This result is a striking example of the contrasting indole reactivity of, on the one hand **1a** and **1b**, and on the other hand **1c**[15]. The relatively fast rate of methanolytic cleaving of **3c** to **1c** and the far higher nucleophilicity of the indole **1c** thus formed in the medium, compared to **1a** or **1b**, are responsible for the preponderant formation of the symmetrical ethene **6c**. Further work on the unusual reactivity and applications of **2c** is in progress.



Scheme 2. Reagent and conditions: *i*: MeOH, 1–2 h, 60 °C; compound **6d** see also lit.[15]

Received: March 13, 1985 [FC 15]

[1] U. Pindur, J. Müller, *Chimia 39* (1985) 142.
[2] J.P. Kutney in J. ApSimon: *Total Synthesis of Natural Products*, Vol. *3*, Wiley-Interscience, New York 1977.
[3] J.E. Saxton: *Indoles Part Four*, Wiley-Interscience, New York 1983.
[4] R.T. Brown, J.A. Joule, P.G. Sammes in D. Barton, W.D. Ollis: *Comprehensive Organic Chemistry*, Vol. *4*, p. 433, Pergamon, Oxford 1979; W.A. Remers in W.J. Houlihan: *Indoles Part Three*, p. 357, Wiley, New York 1979; R. Livingstone in M.F. Ansell: *Rodd's Chemistry of Carbon Compounds*, Vol. *IV*, Suppl. *A*, p. 428, Elsevier, Amsterdam 1984.
[5] S. Hünig, *Angew. Chem. 76* (1964) 400; *Angew. Chem. Int. Ed. Engl. 3* (1964) 548.
[6] B. Oddo, L. Sessa, *Gazz. Chim. Ital. 41* (1919) 237; C. Zatti, A. Ferratini, *Chem. Ber. 23* (1890) 1359; V. Dave, E.W. Warnhoff, *Can. J. Chem. 54* (1976) 1020.
[7] W. Borsche, H. Groth, *Liebigs Ann. Chem. 549* (1941) 238.
[8] S.S. Klioze, F.J. Ehrgott, E.J. Glamkowski, *J. Heterocycl. Chem. 21* (1984) 1257.
[9] J. Bergman, H. Goonewardena, B. Sjöberg, *Heterocycles 19* (1982) 297.
[10] J. Bergman, B. Sjöberg, *Heterocycles 19* (1982) 301.
[11] A. Monge, I. Aldana, I. Lezamiz, E. Fernández-Alvarez, *Synthesis* (1984) 130, and references cited therein.
[12] W.A. Remers in W.J. Houlihan: *Indoles Part One*, p. 111, Wiley-Interscience, New York 1972.
[13] J. Müller, L. Pfeuffer, U. Pindur, *Chem. Ztg. 109* (1985) 15.
[14] E. Akgün, U. Pindur, *J. Heterocycl. Chem. 22* (1985), in press.
[15] U. Pindur, J. Müller, *Chem. Ztg. 108* (1984) 150.