Trimethyl Orthobenzoate as a^1-C_1-Phenyl-Synthon for Functionalization of 3-Unsubstituted Indoles**

Ulf Pindur* and Johann Müller

Abstract: The methylindoles **2a** and **2b** are regioselectively functionalized with trimethyl orthobenzoate at C-3 by means of proton catalysis. The first stage is the formation of the key compounds, 3-indolyl-phenyl-methoxycarbenium ions **3**. These can then be dealkylated under mild conditions using nucleophilic solvent to form the 3-benzoylindoles **5a** and **5b**. The highly stabilized cations **3**, whether generated in situ or directly applied as a salt also represent potent precursors in the derivation of the 3,3′-bisindolyl-phenylmethane dyes **4**.

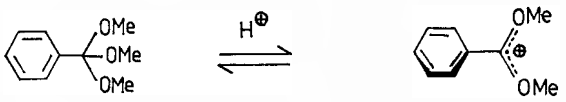
Considering the functionalization of reactive (3-unsubtituted) indoles with S_N1-active orthoesters from the point of view of dialkoxycarbenium ion chemistry, our experimental results led us to propose[1] the following acylation reactivity sequence for acyclic orthoesters using proton catalysis:

$$H{-}C(OEt)_3 > Me{-}C(OEt)_3 > Ph{-}C(OMe)_3 \gg C(OMe)_4$$

The key to the reactivity of these orthoesters with nucleophiles is provided above all by the stability of the corresponding dialkoxycarbenium ions[2] $R{-}C(OAlk)_3 \rightleftharpoons R{-}C(OAlk)_2^{\oplus} + AlkO^{\ominus}$.

Today it is widely accepted[2, 3] that the formation of these oxa-stabilized cations from a defined conformation of orthoesters takes place under stereoelectronic control, which becomes particularly evident after the step whereby acyclic orthoesters (flexible geometry) adapt to a cyclic structure with more rigid geometry (e.g. in the case of 1,3-dioxolane type)[4]. The minimum of reactivity is achieved with tetramethyl orthocarbonate which under conditions of proton catalysis forms no C–C-bonds even with reactive indoles[1]. This is due to the fact that the corresponding alkoxycarbenium ion, generated in situ, is extremely stabilized in the ground state.

In this series, although trimethyl orthobenzoate is among the less reactive *C*-electrophiles, since no reaction occurs with indoles of lower nucleophilicity (e.g. 3-methylindoles), nevertheless reaction does take place with simple 3-unsubstituted indoles, e.g. **2a** and **2b.** The hydrolysis rates obtained from numerous kinetic measurements may be used as empirically substantiated reactivity parameters for orthoesters. Trimethyl orthobenzoate **1a** shows a low hydrolysis rate compared with triethyl orthoformate and triethyl orthoacetate; its lower reactivity is predominantly attributable to a sterically determined suppression of conjugation in the cation **1b**[4].



1a **1b**

The acylation potential of **1a** in the presence of at least equal molar quantities of a proton acid is, however, still adequate to permit reaction with the indoles **2a** and **2b**.

Here we report on variable functionalization at the indole skeleton with the S_N1-active orthoester **1a**. The indoles **2a** and **2b** react with **1a** in dichloromethane when tetrafluoroborate-ether is added, to produce the highly stabilized 3-indolyl-phenylmethoxycarbenium ions **3a** and **3b**. The BF_4-salt of **3a** precipitates almost quantitatively in the aprotic medium, whilst diethylether or hexane must be added in order to isolate the salt of **3b**. These cations represent a key compound for several interesting offshoot reactions.

One characteristic of the reactivity of stabilized alkoxycarbenium ions is the dealkylation – normally thermodynamically controlled – by means of nucleophiles[5]. In fact, the ambident cations **3** can be transformed almost quantitatively into the 3-benzoylindoles **5** under mild conditions with peripheral dealkylation by methanol (route *a*). In our first communication[1] we had already noted this reaction under in situ condition from the aspect of mechanism, without, however, attempting a characterization of the interesting cations **3**. The present results unequivocally document the fact that trimethyl orthobenzoate is particularly well adapted as a «new» reagent for regioselective functionalization of the indole nucleus. In principle, benzoylation can also be achieved using other acylation equivalents, such as benzoyl chloride[6], 2-phenyl-4,5-dihydroimidazole/Ac_2O[7], *N*,*N*-dimethylbenzamide/$POCl_3$[8] or via 2-(3-indolyl)-2-penyl-1,3-dithiane[9]. However, it is evident that our alternative, due to its extreme practical simplicity, the high degree of regioselectivity, and the relatively mild conditions, is superior to the other methods enumerated.

A considerably more regioselective nucleophilic attack at the carbenium centre of the ambident cation **3** can be achieved by using relatively strong nucleophiles, especially in the presence of solvents with relatively weak nucleophilicity or practically none at all, in order to avoid competitive reactions. This reaction path (route *b*) is subject to kinetic control[5]. If, for example, the starting compounds **2a** and **2b** are offered as relatively strong nucleophiles then, with proton catalysis the 3,3′-bisindolyl(aryl)methylium ions **4a** and **4b** of rosindole type will be obtained (yield 35 and 60%). This reaction can follow either of two different ways regarding the mechanistic aspect.

In an aprotic solvent without nucleophilic potential the dyes **4** derive directly from **3** by the formal S_N-reaction with the indoles **2** (route *b*). This step depends first and foremost on the solubility of the reactants. The second reaction path proceeds by way of the 3-benzoylindoles **5**, which can either be produced in methanol from **3** in situ (route *a*), or else can serve directly

* *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 5. – Part 4: J. Müller, L. Pfeuffer, U. Pindur, *Monatsh. Chem. 116* (1985) 365.

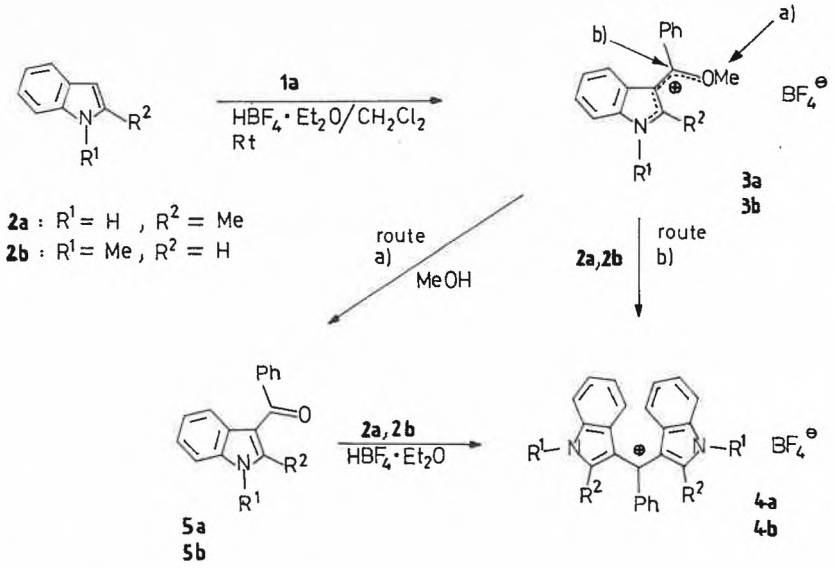


Table 1. Experimental data and yields for the functionalized indoles **3–5**.

Compound[a]	(M_r)	m/z (M^+)	Yield [%]	Method[b]
3a	$C_{17}H_{16}BF_4NO$ (337.12)	249 ($M^+ - HBF_4$)	92	A
3b	$C_{17}H_{16}BF_4NO$ (337.12)	249 ($M^+ - HBF_4$)	90	B
4a	$C_{25}H_{21}BF_4N_2$ (436.26)	348 ($M^+ - HBF_4$)	35	C
4b	$C_{25}H_{21}BF_4N_2$ (436.26)	348 ($M^+ - HBF_4$)	60	D
5a	$C_{16}H_{13}NO$ (235.28)	235	77–85	E
5b	$C_{16}H_{13}NO$ (235.28)	235	80–90	E

[a] The elemental analyses of the compounds **3–5** were within the margin of error (± 0.3%) correct and the IR-, ^{1}H- and ^{13}C-NMR-spectroscopic data correspond to the formulated constitutions. **5a** and **5b** are already described in lit. [8b].

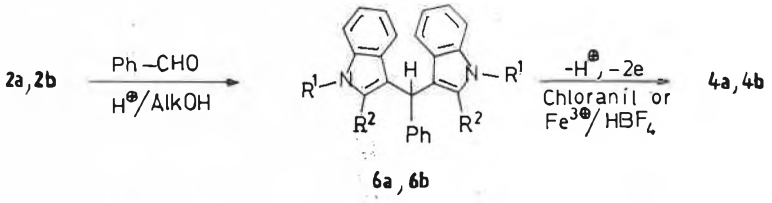
[b] Methods: A: **2a**, **1a** (1:1), $HBF_4 \cdot Et_2O$, CH_2Cl_2, r.t., 1h.
B: **2b**, **1a** (1:1), $HBF_4 \cdot Et_2O$, CH_2Cl_2, r.t., 1h (dimeric **2b** is byproduct); Et_2O or *n*-hexane (excess).
C: **3a**, **2a** (1:1), $HBF_4 \cdot Et_2O$, MeOH, r.t., 12 h (via **5a**).
D: **3b**, **2b** (1:1), $HBF_4 \cdot Et_2O$, CH_2Cl_2, r.t., 12h or **3b**, **2b** (1:1), $HBF_4 \cdot Et_2O$, MeOH, r.t., 12h (via **5b**).
E: **3a** or **3b**, MeOH, r.t., 1h or **2a** or **2b** and **1a** (1:1), $HBF_4 \cdot Et_2O$, 1) CH_2Cl_2, 2) MeOH, r.t., 2h.

as starting compound. In the presence of HBF_4-ether, finally, the *O*-protonized form of **5** reacts with **2**. This final step, and also the route *b*, proceed in accordance with the same mechanism.

The method here described for deriving heteroanalogous methane dyes should, in principle, be applicable to other, suitable, reactants (e.g. substituted ortho arylesters, nucleophilic heteroarenes). This should open a large variety of ways to derive this still scarcely studied class of dyes[10].

In order to confirm the structure and establish the advantages of our synthetic method we also independently synthesized the dyes **4** in the «classical» way by means of indole/benzaldehyde/$H^{\oplus}$-condensation, and the subsequent step, so hard to control, where the leucobases **6a** and **6b**, formed as intermediate substrates are oxidized[11].

The preparative results from this independent method justify our contention that the synthetic approach we have here presented to deriving **4**, bearing in mind the prospect of deriving other analogous compounds, is of interest and promise for the chemistry of heteroarylmethane dyes.



Received: December 17, 1984 [FC 9]

[1] E. Akgün, U. Pindur, J. Müller, *J. Heterocycl. Chem. 20* (1983) 1303.
[2] S. Chandrasekhar, A.J. Kirby, R.J. Martin, *J. Chem. Soc. Perkin Trans. II* (1983) 1619; A.J. Kirby, *Acc. Chem. Res. 17* (1984) 305.
[3] P. Deslongchamps in J.E. Baldwin, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Oxford 1983, p. 72 ff.
[4] Y. Chiang, A.J. Kresge, P. Salomaa, C.I. Young, *J. Am. Chem. Soc. 96* (1974) 4494; O. Bouab, G. Lamaty, C. Moreau, O. Pomares, P. Deslongchamps, L. Ruest, *Can. J. Chem. 58* (1980) 567.
[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* (1911) 234.
[7] J. Bergman, H. Goonewardena, B. Sjöberg, *Heterocycles 19* (1982) 297.
[8] a) W.C. Anthony, *J. Org. Chem. 25* (1960) 2049; b) J. Szmuskovicz, *ibid. 27* (1962) 511.
[9] P. Stütz, P.A. Stadler, *Org. Synth. 56* (1977) 8; R. Livingstone in M.F. Ansell: *Rodd's Chemistry of Carbon Compounds*, Vol. *IV*, Elsevier, Amsterdam 1984, p. 428.
[10] R. Naef, *Dyes Pigments 2* (1981) 57.
[11] W.A. Remers in W.J. Houlihan: *Indoles, Part One*, Wiley-Interscience, New York 1972, p. 105; R. von Walther, J. Clemen, *J. Prakt. Chem. 61* (1900) 257; A. Étienne, R. Heymès, *Bull. Soc. Chim. Fr.* (1948) 841; M. Freund, G. Lebach, *Chem. Ber. 38* (1905) 2646.