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THE REACTION OF INDOLE AND PYRROLE WITH IMIDAZOLE-Ac_2O-REAGENTS. A NOVEL SYNTHESIS OF ALDEHYDES.

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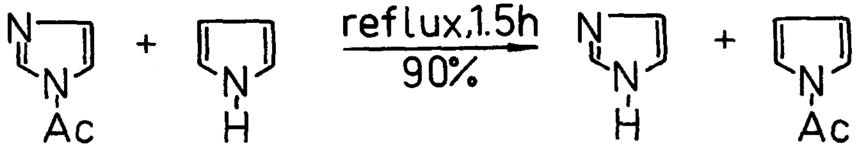
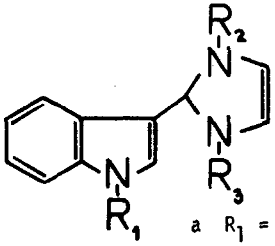
N-acylimidazoles are standard reagents for preparative transacylations.[1] An example[2] is given below.



In a routine preparation of N-acetylindole by such a transacetylation an unexpected nonbasic (insoluble in 2 M HCl) minor product, with the composition $C_{15}H_{15}N_3O_2$, was isolated. By changing the procedure (slow addition of indole in Ac_2O to a solution of imidazole or N-acetylimidazole in Ac_2O at 125°) it became the major product.

The NMR spectrum in DMSO at 70° showed the acetyl protons as a strong singlet, but at 30°, as an unsymmetrical quartet due to hindered rotation about the N-$COCH_3$ bonds. The UV-spectrum is similar to that of indole. The C=O vibration (KBr disk) occurred at 1655 cm^{-1} which is too low for an N-acetylated indole. (The C=O frequency of, e.g., N-acetyl-3-methyl-indole was at 1691 cm^{-1}.) These facts suggest that the product has structure **1a** rather than structure **1b** or **2**. Acetylation of **1a** gave **1c**. When imidazole-Ac_2O was replaced by thiazole-Ac_2O compound **3** was obtained.

The formation of **1a** from indole and an imidazole-Ac_2O reagent may be explained by an electrophilic attack in the 3-position of indole by a N,N-diacetylimidazolium ion formed by the following equilibrium:

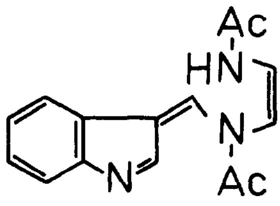


a R_1 = H R_2 = R_3 = Ac

b R_2 = H R_1 = R_3 = Ac

c R_1 = R_2 = R_3 = Ac

1



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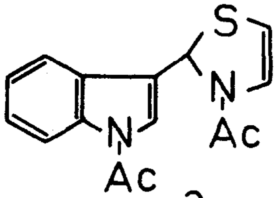

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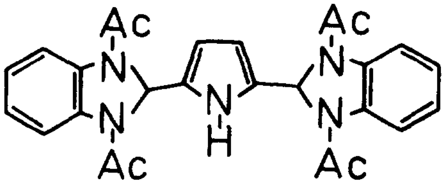

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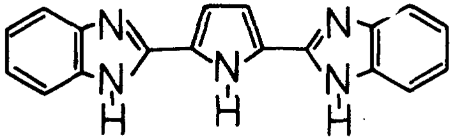

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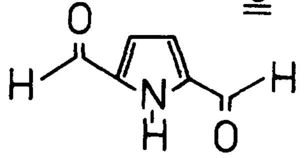

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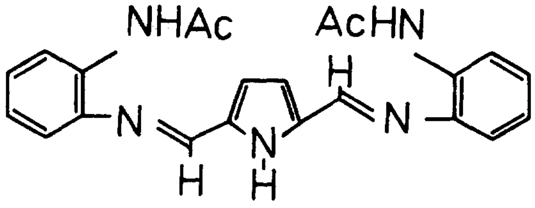

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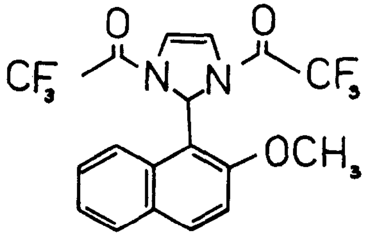

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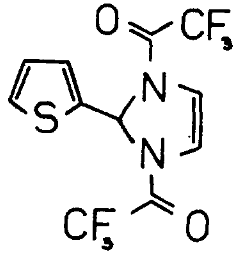

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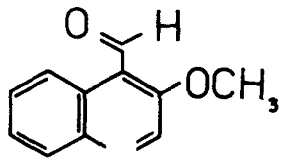

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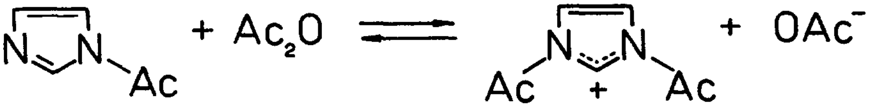
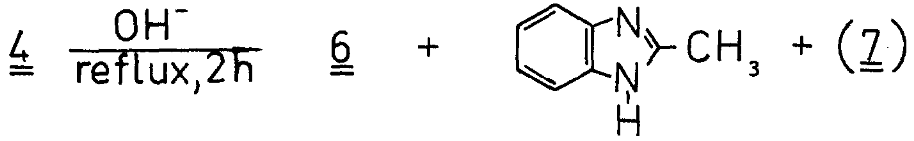


The dihydroimidazole ring in **1a** is readily ruptured by nucleophilic reagents. Thus, heating (120°) with indole in Ac_2O gave tris-(3-indolyl)methane; and mild hydrolysis with NaOH in ethanol/water gave 3-formylindole in good yield. To account for the easy formation of tris-(3-indolyl)methane it is suggested that the equilibrium, **1a** ⇄ **2**, is set up. Indole then adds to **2**, and the resultant species is cleaved and the indole-addition repeated. The ring-opening, **1a** → **2**, may be looked upon as an intramolecular Bamberger cleavage.[3]

Other aromatics, easily susceptible to electrophilic substitution, such as *N*,*N*-dimethylaniline, 1,2,4-trimethoxybenzene, 2-methoxynaphthalene, anthracene, thiophen, pyrrole and ferrocene, failed to react when subjected to the action of a refluxing Ac_2O-imidazole reagent, except *N*,*N*-dimethylaniline, which gave tris-(4-dimethylaminophenyl)methane (leuco crystal violet) in good yield, and pyrrole, which gave *N*-acetylpyrrole. By replacing imidazole with benzimidazole, pyrrole gave a product (yield, 94 %), which has been assigned structure **4**, as the known[4] compound **5**, when hydrogenated in Ac_2O (95°), also gave **4**. Only small amounts (~ 0.5 %) of *N*-acetylpyrrole were formed along with **4** in the substitution reaction. The great difference between the two reagents seems to depend on the fact that *N*-acetylimidazole is a more powerful transacetylation reagent than *N*-acetylbenzimidazole, rather than on a considerably higher reactivity of the *N*,*N*-diacetylbenzimidazolium ion compared with the *N*,*N*-diacetylimidazolium ion.

In a supplemental experiment it was found that pyrrole was *N*-acetylated about four times more rapidly with *N*-acetylimidazole than with *N*-acetylbenzimidazole.

Alkaline hydrolysis of **4** gave the known[5,6,7] 2,5-diformylpyrrole (**6**) in fair yield (40 %) together with secondary products. The desired product could, however, be easily isolated by column chromatography (SiO_2, CH_2Cl_2). Compound **7**, which can conveniently be isolated by interrupting the hydrolysis after 45 minutes, is an intermediate in the formation



of **6**. The 2-methylbenzimidazole is probably formed by intramolecular condensation of the hydrolysis product 2-aminoacetanilide (cf. ref. 8).

The reactivity of the reagent can be enhanced by replacing the acetic anhydride with trifluoroacetic anhydride. With an imidazole trifluoroacetic anhydride reagent, e.g., 2-methoxynaphthalene and thiophen gave **8** and **9** respectively. Alkaline hydrolysis of **8** gave **10** together with products formed in secondary (Cannizzaro) reactions.

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7. I wish to thank Dr. P. Fournari (Dijon, France) for a sample of 2,5-diformylpyrrole, prepared by his yet unpublished procedure.[6] [Cf. the related procedure for 2,4-diformylpyrrole; P. Fournari, M. Farnier and C. Fournier, Bull. Soc. Chim. France, 283 (1972)].
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