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Synthesis of Functionalized 1-Vinylazoles by a Novel Wittig Reaction of 1-Acylazoles

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Abstract: Wittig reaction of aromatic and heteroaromatic 1-acylimidazoles, 1-acyl-1,2,4-triazoles, and 1-acylbenzimidazoles with acceptor-stabilized phosphoranes was found to be a convenient method for the preparation of the E isomers of 1-vinylazoles. Copyright © 1996 Elsevier Science Ltd

Imidazole and 1,2,4-triazole derivatives are under development as inhibitors of the cytochrome P-450 aromatase for the use in tumor therapy.¹ Since these compounds are mostly chiral we synthesized highly active vinylazoles lacking chirality² and in this connection we also looked for vinylazoles bearing acceptor groups at the double bond. First tests of compounds **3** had shown that the E isomers were pharmacologically more active, therefore a good method for their synthesis was required. The known methods^{3,4} resulted in mixtures with a low E isomer content, a result which is consistent with the literature.⁵ In contrast to the known acylation of the phosphoranes **2** ($\mathbb{R}^2 = \mathbb{H}$, alkyl) with aliphatic acylimidazoles⁶ (**path B**), we found that in the reaction of aromatic and heteroaromatic acylazoles 1 with acceptor-stabilized phosphoranes the normal Wittig products **3** were formed (**path A**).



The products obtained by this method (Table I) contain 50-70% of the E isomers 3 confirmed by NMR NOE experiments with the exception of the *ortho* fluoro derivative 3d, where 75% of the Z isomer were formed. The ratio of the isomers was easily determined by the different chemical shift of the olefinic protons in the ¹H NMR spectra.⁷

In a typical procedure the appropriate N-trimethylsilyl azole (1.1 mmol) and the aroyl chloride (1.0 mmol) in 5 ml of tetrahydrofuran are left at room temperature for 30 minutes, all volatile components are removed *in vacuo* (0.1 mbar) and the residue is dissolved in 5 ml of tetrahydrofuran. After addition of the phosphorane 2 (1.5 mmol) the mixture is refluxed for 6 hours. The crude product is purified by chromatography on silicagel (dichloromethane/ methanol 98:2) or by recrystallization from cyclohexane or *tert*.butyl methyl ether.

In accordance with the literature⁸ we could not observe Wittig reactions with non-stabilized phosphoranes or with phosphonates even when stabilized by an acceptor group. Benzoylimidazoles with strong electron donating substituents at the phenyl ring (e.g. 4-OCH₃) or with a nitro group in the *ortho* position gave only acylation products 4, likewise no reaction according to path A was observed with indole or benzotriazole. The reaction conditions of stabilized phosphoranes with acylazoles are considerably milder than those recently described for lactones.⁹



a. IM = 1-imidazolyl, TRI = 1(1,2,4-triazolyl), BI = 1-benzimidazolyl; b. Overall yield based on the aroyl chloride used; c. Not optimized yields of the E/Z mixture; d. Melting point of the pure E isomer; e. The E/Z ratio is 25:75 in this case, the mp given is that of the Z isomer.

In spite of some limitations our method offers a rapid access to functionalized vinylazoles from commercially available or easily accessable starting materials in a two step procedure without isolation of intermediates involving easy purification of the E isomers.

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References and Notes

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