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

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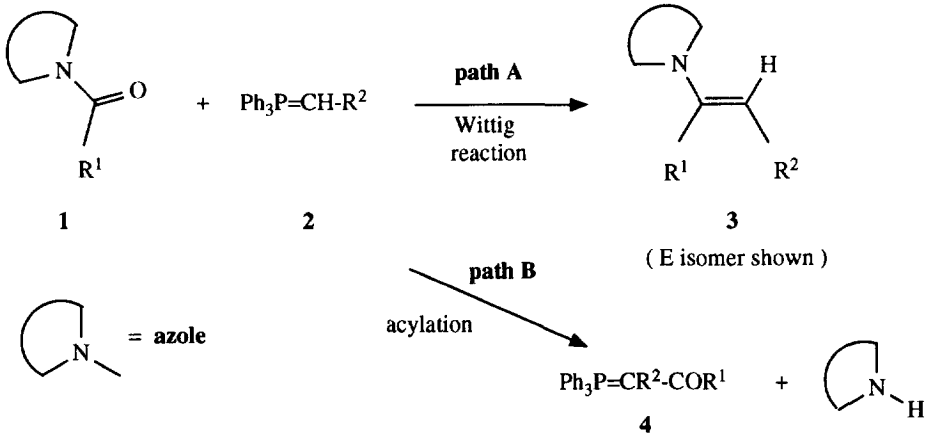
Abstract: Wittig reaction of aromatic and heteroaromatic 1-acylimidazoles, 1-acyl-1,2,4-triazoles, and 1-acylbenzimidazoles with acceptor-stabilized phosphoranes was found to be a convenient method for the preparation of the E isomers of 1-vinylazoles.

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 chirality[2] 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** (R^2 = H, alkyl) with aliphatic acylimidazoles[6] (**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**).

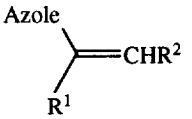


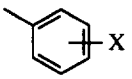
The products obtained by this method (Table I) contain 50-70% of the E isomers **3** confirmed by NMR NOE experiments with the exception of the *ortho* fluoro derivative **3d**, where 75% of the Z isomer were formed. The ratio of the isomers was easily determined by the different chemical shift of the olefinic protons in the ^{1}H 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 literature[8] 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-OCH_3) 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]

Table I. Wittig Products **3**



Entry	R^1	R^2	Azole [a]	Yield (%)[b,c]	mp (°C) [d]
3a	 X = H	$COOCH_3$	IM	77	106 - 107
3b	4 - Br	$COOC(CH_3)_3$	IM	75	131 - 132
3c	4 - CF_3	$COOC(CH_3)_3$	IM	59	96 - 101
3d	2 - F	$COOC(CH_3)_3$	IM	29	90 - 94 [e]
3e	4 - CN	CN	IM	27	188 - 193
3f	4 - CN	$COCH_2C(CH_3)_3$	IM	50	166 - 168
3g	4 - CN	$COOCH_3$	TRI	15	141 - 142
3h	4 - CN	$COOCH_3$	BI	7	158 - 162
3i	4 - pyridyl	$COOC(CH_3)_3$	IM	56	127 - 130

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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7. Chemical shifts of the olefinic proton (δ [ppm]; E isomer / Z isomer) *in* $CDCl_3$: **3a** 6.15/6.25; **3d** 6.07/6.15; **3f** 6.50/6.48; **3g** 6.90/6.97; **3h** 6.42/6.53; **3i** 6.17/6.39; *in* $DMSO\text{-}D_6$: **3b** 6.33/6.52; **3c** 6.43/6.55; **3d** 6.32/6.52; **3e** 6.50/6.65; **3i** 6.45/6.80.
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