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Catalysis and Regioselectivity in the Michael Addition of Azoles. Kinetic *vs.* Thermodynamic Control

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Abstract: Bicyclic guanidine bases, TBD and MTBD were found to be highly efficient catalysts in the Michael addition of azoles with α,β-unsaturated nitriles and esters. The factors influencing regioselectivity have been elucidated, and some new azole-Michael adducts were synthesized. These were shown to be useful starting compounds for the regioselective *N*-alkylation of the corresponding azoles.

Michael adducts are useful starting compounds for obtaining the thermodynamically less stable regioisomers of various *N*-substituted azoles, compounds with diverse pharmacological uses.[1] Since overall efficiency of that procedure is mainly dependent on the outcome of the *N*-protective step (*i.e.* the Michael addition) we found it worthy to study the factors influencing the yield and regioselectivity of the Michael addition of azoles.

Though azoles with higher nucleophilicity, such as imidazole, *C*-alkyl imidazoles and 1,2,4-triazole react fairly well with Michael acceptors without any catalyst, reaction of azoles with lower nucleophilicity proceeds very sluggishly, and catalysts such as pyridine,[2,3] triethylamine,[4,5] tetraalkylammonium hydroxides,[2,4,6-8] KOH[9,10] or MeONa[11,12] were employed. Our investigations indicated that while triethylamine and pyridine showed low efficiency in most of the cases, other bases lead to considerable amounts of byproducts (e.g. by alcohol addition or polymerization) due to their nucleophilic character.

In the present study, we found the commercially available strong, bicyclic guanidine bases, TBD and MTBD to be excellent catalysts for the reaction of azoles with α,β-unsaturated nitriles and esters (Table 1):

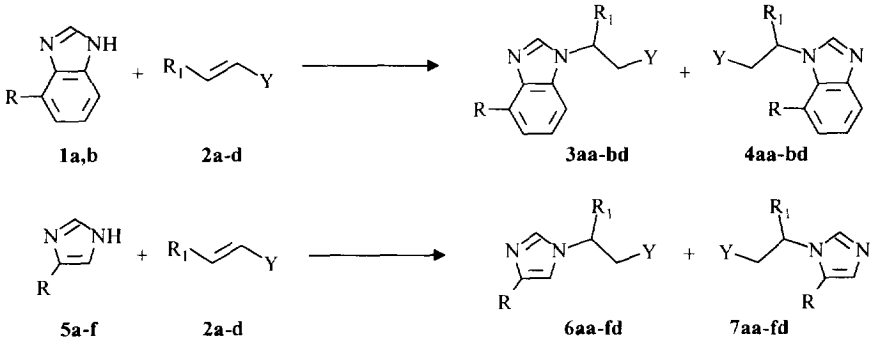
Table 1. Comparative data on the addition of some azoles to acrylonitrile

Azole	Acrylonitrile (eq.)	Solvent	Catalyst	t (°C)	τ (hours)	Isolated yield (%)	Lit.
Benzimidazole	2.5	EtOH	$PhNMe_3OH$	40		83	6
		acrylonitrile	$BnNMe_3OH$	25	24		13
		acrylonitrile	Et_3N	76	90	72	14
	1.2	MeCN	MTBD[a]	25	1	91	14
4-Phenyl-imidazole	3	EtOH	KOH	78	2	54	9
	1.2	MeCN	TBD[b]	25	0.15	95	14
4-Nitro-imidazole	1.2	DMSO	pyridine	140	10	90	3
	1.2	MeCN	MTBD	80	3	92	14

[a] Aldrich no. 35,950-5; [b] Aldrich no. 34,557-1

In the presence of 1-5 mol % TBD or MTBD in acetonitrile solution, the Michael-additions proceeded faster even at lower temperatures, and no side reactions could be detected. The azole-Michael adducts could be isolated in higher yields and purity when compared to literature methods.[15]

Systematic studies on regioselectivity of Michael additions of imidazoles and benzimidazoles are scarce, except for reports on 2,4-dialkylimidazoles,[16] 5-nitrobenzimidazoles[17] and 4-nitroimidazoles.[3] The present study extends to the Michael additions of the most common α,β-unsaturated nitriles and esters with imidazoles and benzimidazoles bearing various 4-substituents (Table 2):



Scheme 1

Table 2. Ratio of **3** : **4** (1,4 to 1,7 adducts) and **6** : **7** (1,4 to 1,5 adducts) in the TBD-catalyzed Michael addition of azoles at room temperature in MeCN as solvent, determined by ^{1}H NMR of crude products

Azole	Substituent		**2a**	**2b**	**2c**	**2d**
	R	Effect	Acrylonitrile	Et-acrylate	Crotononitrile	Me-crotonate
1a[a]	NO_2	-E, -I	~ 100 : 0[b]	> 99 : 1	~ 100 : 0	~ 100 : 0
1b	Me	+I	86 : 14	81 : 19	> 99 : 1[b]	90 : 10
5a[c,d]	NO_2	-E, -I	~ 100 : 0[b]	> 99 : 1	~ 100 : 0	> 99 : 1
5b	$CH=CHCO_2Et$	-E, -I	~ 100 : 0[b]	> 99 : 1	~ 100 : 0	> 99 : 1
5c	Ph	+E, -I	> 99 : 1[b]	88 : 12	~ 100 : 0	97 : 3
5d[18,d]	$CH=CHCMe_2OH$	+E, -I	80 : 20	75 : 25	93 : 7	89 : 11
5e[d]	$(CH_2)_2CO_2Et$	+I	72 : 28	65 : 35	88 : 12	82 : 18
5f[e]	Me	+I	63 : 37	63 : 37	81 : 19[b]	81 : 19

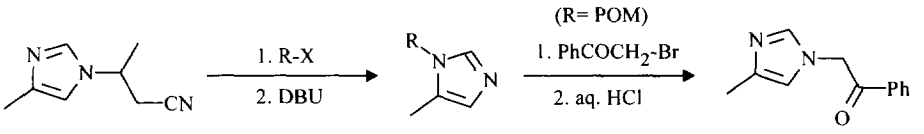
[a] Reactions in **2** as solvent in the presence of 1 eq. of DMAP at 80 °C; [b] Isolated yields: **3aa**: 88 %, **3bc**: 96 %, **6aa**: 92 %, **6ba**: 92 %, **6ca**: 95 %, **6fc oxalate**: 65 %; [c] Reaction at 80 °C; [d] Catalyst: MTBD; [e] Without catalyst at 80 °C

We found that TBD-catalyzed addition of acrylonitrile and crotononitrile was more selective in most cases than addition of the corresponding α,β-unsaturated esters. To elucidate the origin of this observation, first, we proved (by ^{1}H NMR in CD_3CN solution) that TBD reacts rapidly with an equivalent of acrylonitrile or ethyl acrylate to form the corresponding Michael addition products (TBD-MAs): 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-a]pyrimidine-1-propanoic acid derivatives (nitrile and ethyl ester, respectively).

The *in situ* formed TBD-MAs were then reacted with an equivalent of azole (4-phenyl-imidazole or 4-methyl-benzimidazole). While reactions of cyanoethyl-TBD at 30 °C proceeded slowly towards equilibrium mixtures containing the azole, azole-MA, TBD and TBD-MA, no reaction was observed with (ethoxy-carbonyl)ethyl-TBD in the 30-70 °C temperature range. Moreover, reaction of the cyanoethyl-azoles with an equivalent of TBD proceeded towards the same equilibrium mixtures, while the azole-ethyl acrylate adducts did not react with TBD, demonstrating that TBD-catalyzed reactions of 4-phenyl-imidazole and 4-methyl-

benzimidazole with acrylonitrile are reversible, while additions of ethyl acrylate are irreversible. Thus, the regioselectivity data reflect *thermodynamic control* for the α,β-unsaturated nitriles and *kinetic control* in the case of the α,β-unsaturated esters. This is true for all azoles studied (except for **5f**, with all four reactions thermodinamically controlled under the conditions stated), as it was checked by reacting the isolated adducts with TBD.

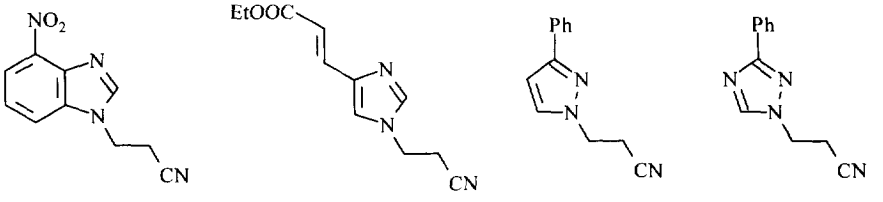
Compounds **3bc**, **6aa** and **6ca** were already shown to be useful substrates for obtaining *N*-substituted derivatives of the parent azoles **1b**, **5a** and **5c**, respectively. Derivatives of **5e** are accessible comfortably from **6ea** obtained by hydrogenation of **6ba** over Pd/C (96 % yield). The most reluctant case,[1] the regioselective alkylation of 4-methyl-imidazole could be solved using conventional separation techniques: the pure 1,4-adduct of 4-methyl-imidazole and crotononitrile (α,4-dimethyl-1*H*-imidazole-1-propanenitrile, **6fc**) was obtained by fractional crystallization of the adduct mixture as the oxalate salt. Compound **6fc** provides an easy access to both 1-substituted-5- (**8a**: R= benzyl and **8b**: R= pivaloyloxymethyl) and 1-substituted-4-methyl-imidazoles (*e. g.* 1-phenacyl-4-methyl-imidazole **9**):[19]



6fc **8a,b** **9**

Scheme 2

The efficient catalysis of the Michael additions of azoles by the guanidine bases was used in the high-yield preparation of the previously unknown cyanoethyl derivatives of 4-nitrobenzimidazole **3aa**, urocanic acid ethyl ester **6ba**, 3-phenyl-pyrazole **10** and 3-phenyl-1,2,4-triazole **11** (Scheme 3) in thermodynamically



3aa **6ba** **10** **11**

Scheme 3

controlled reactions with acrylonitrile. These adducts are useful starting compounds for the preparation of the thermodynamically less stable *N*-substituted derivatives of the parent azoles: quaternization (with allyl bromide or dimethyl sulfate, respectively) followed by deprotection afforded the known 1-methyl-7-nitro-benzimidazole[20] (yield: 75 %), *E*-1-(2-propenyl)-1*H*-imidazole-5-propenoic acid ethyl ester (or N^{π}-allyl urocanic acid ethyl ester[21]) (89 %), 1-methyl-5-phenyl-1*H*-pyrazole[22] (60 %) and 4-methyl-3-phenyl-4*H*-1,2,4-triazole[23] (64 %), respectively.

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15. **3aa**: mp 195-196 °C (acetone). ^{1}H NMR (200 MHz) (DMSO-d_6): 3.19 (t, 2H), 4.72 (t, 2H), 7.52 (t, 1H), 8.10 (dd, 1H), 8.25 (dd, 1H), 8.63 (s, 1H). MS (EI$^+$, 70 eV): m/z (%): 216 (M$^+$, 100), 186 (68), 146 (33), 118 (94). **6ba**: mp 120-121.5 °C (EtOH). ^{1}H NMR ($CDCl_3$): 1.31 (t, 3H), 2.84 (t, 2H), 4.16-4.33 (m, 4H), 6,57 (d, 1H, *J*= 15 Hz), 7.22 (m, 1H), 7.55 (d, 1H, *J*= 15 Hz), 7.59 (m, 1H). MS: 219 (M$^+$, 27), 174 (100), 147 (46), 105 (25). **6fc oxalate**: mp 104-105.5 °C (EtOH). ^{1}H NMR (DMSO-d_6): 1.51 (d, 3H, *J*= 6.8 Hz), 2.20 (d, 3H, *J*= 0.9 Hz), 3.17 (d, 2H, *J*= 6.6 Hz), 4.77 (sext, 1H, *J*= 6.7 Hz), 7.38 (m, 1H), 8.51 (d, 1H, *J*= 1.5 Hz). MS: 149 (base M$^+$, 48), 109 (100), 81 (43). **10**: yield: 95 %, mp 51-53 °C (petr. ether : toluene 2:1). ^{1}H NMR ($CDCl_3$): 3.00 (t, 2H), 4.42 (t, 2H), 6.57 (d, 1H, *J*= 3.0 Hz), 7.30-7.47 (m, 3H), 7.52 (d, 1H, *J*= 3.0 Hz), 7.78 (m, 2H). MS: 197 (M$^+$, 43), 157 (79), 144 (9), 130 (24), 77 (100), 63 (23), 51 (78). **11**: yield: 86 %, mp 86.5-88 °C (H_2O : EtOH 1:1). ^{1}H NMR ($CDCl_3$): 3.04 (t, 2H), 4.46 (t, 2H), 7.37-7.52 (m, 3H), 8.03-8.15 (m, 2H), 8.20 (s, 1H). MS: 198 (M$^+$, 100), 158 (8), 145 (7), 131 (42), 104 (34), 77 (19).
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18. Compound **5d** was obtained in 45 % yield by reaction of urocanic acid ethyl ester with excess MeMgI in ether, mp 133-137 °C (EtOAc). ^{1}H NMR (DMSO-d_6): 1.24 (s, 6H), 4.59 (OH), 6.22 (d, 1H, *J*= 16 Hz), 6.37 (d, 1H, *J*= 16 Hz), 6.98 (m, 1H), 7.57 (m, 1H). MS: 152 (M$^+$, 11), 133 (100), 119 (32).
19. **8b**: yield: 52 %, colourless oil. ^{1}H NMR ($CDCl_3$): 1.18 (s, 9H), 2.27 (d, 3H, *J*= 1.0 Hz), 5.80 (s, 2H), 6,78 (m, 1H), 7.61 (m, 1H). MS: 196 (M$^+$, 7), 95 (20), 94 (28), 57 (100). **9**: yield 94 %, mp 121-124 °C (petr. ether : EtOAc 2:1). ^{1}H NMR ($CDCl_3$): 2.28 (m, 3H), 5.32 (s, 2H), 6.66 (m, 1H), 7.41 (m, 1H), 7.47-7.73 (m, 3H), 7.99 (m, 2H). MS: 200 (M$^+$, 13), 105 (100), 77 (38).
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