Mannich Reactions of Carbonyl Compounds and Enamines with Benzotriazole as the NH Component

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Boron trifluoride catalyses reactions of 1-(hydroxymethyl)benzotriazole with ketones to give predominantly monosubstituted Mannich products. In unsymmetrical ketones, a methylene is slightly more reactive than a methyl group. For 1,3-diketones and diethyl malonate, substitution occurs on the central methylene group. β-Aminocrotononitrile and β-aminocrotonate undergo Mannich condensations with benzotriazole and formaldehyde without any catalyst. Preliminary investigations of the reactivity of the Mannich bases thus obtained are reported.

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Introduction.

1-(Hydroxymethyl)benzotriazole [1] (**1**) condenses with a wide variety of NH- compounds producing the corresponding *N*-(benzotriazol-1-ylmethyl) derivatives. The benzotriazolyl moiety of these products can be easily substituted by a hydrogen atom (reduction), an alkyl group (Grignard reaction), or other nucleophiles leading to versatile synthetic methods for, *inter alia*, *N*-mono- and *N,N*-dialkylated amines, hydrazines, hydroxylamines and amides [2].

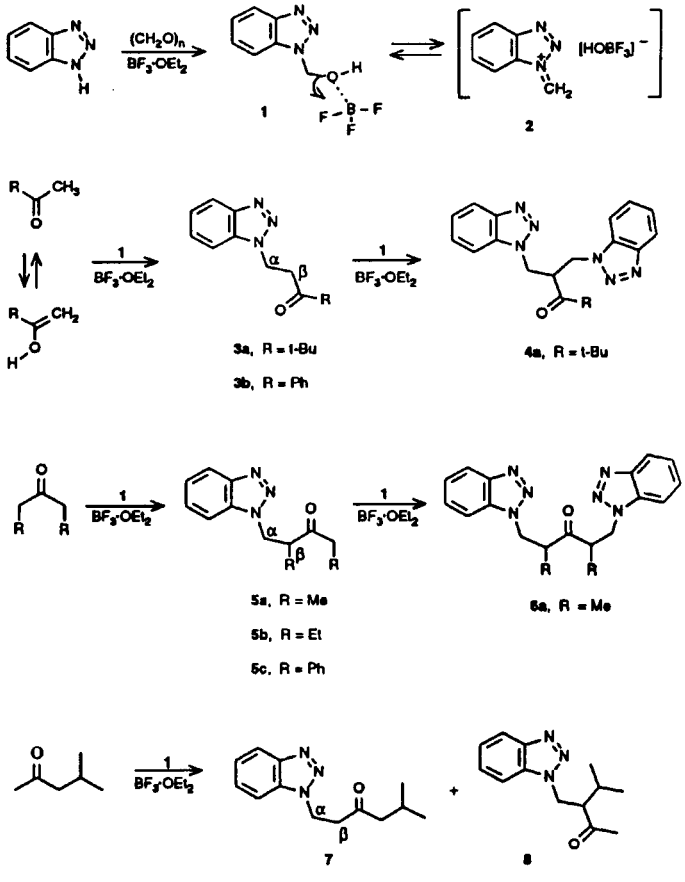
Immonium cations **2** derived from benzotriazole are much less stabilized then immonium intermediates in typical Mannich reactions [3] (benzotriazole is a very weak base, p*K*a 1.6 [4]). Therefore **1** should react (under acidic catalysis) even with weak nucleophiles: indeed, Ritter reactions of **1** with nitriles catalysed by boron trifluoride give the corresponding *N*-(benzotriazol-1-yl)methylated amides [5]. We now report reactions of **1**, formed *in situ* from benzotriazole and paraformaldehyde, with carbon nucleophiles derived from ketones and from 1,3-dicarbonyl compounds, and with enamines stabilized by an adjacent cyano or carboethoxy group.

Results and discussion.

Ketones.

t-Butyl methyl ketone with benzotriazole and paraformaldehyde in the presence of boron trifluoride gave a mixture, separated by column chromatography, of 1-(benzotriazol-1-yl)-4,4-dimethyl-3-pentanone (**3a**) and 1-(benzotriazol-1-yl)-2-(benzotriazol-1-yl)methyl-4,4-dimethylpentanone (**4a**) in a ratio of 78:22 and a total yield of 51% (Scheme 1). From a similar reaction with acetophenone, only the monobenzotriazolylmethylated product **3b** was obtained. As in other Mannich reactions, condensation of **1** with ketones is believed to proceed *via* a nucleophilic attack of cation **2** on the enol form of the ketone.

Scheme 1



In symmetrical dialkyl ketones, the reaction could occur on both α-carbon atoms giving mono- **5** and disubstituted derivatives **6**. Use of equimolar amounts of benzotriazole, paraformaldehyde and ketone gave, after separation by column chromatography, the monosubstituted derivatives in satisfactory yields (61% for **5a**, Table 1). In general, products **5** were contaminated with small amounts of **6**, the starting materials and complex molecules deriving from self condensation of the starting

ketone. An excess of benzotriazole and paraformaldehyde in a reaction with 3-pentanone gave disubstituted product **6a** in only 20% yield. Apparently, the presence of a (benzotriazol-1-yl)methyl group in the molecule has a retarding effect on further Mannich reactions.

In the case of unsymmetrical ketones with two reactive

Table 1

Products of the Mannich Reaction of Benzotriazole with Carbonyl Compounds **3-8** and **14**

No.	Yield (%)	Mp (°C)	Solvent [a]	Formula	Elemental Analysis (%) Found C	Found H	Found N	Calcd. C	Calcd. H	Calcd. N
3a	40 [b]	198-199 [c]	$CHCl_3$	$C_{13}H_{17}N_3O$	55.08 [c]	5.07 [c]	23.71 [c]	55.47 [c]	5.15 [c]	23.83 [c]
3b	32	70-71	MeOH	$C_{15}H_{13}N_3O$	71.85	5.35	16.38	71.70	5.21	16.72
4a	11 [b]	oil	-	$C_{20}H_{22}N_6O$	[d]	[d]	[d]	[d]	[d]	[d]
5a	61	170 [c]	$CHCl_3$	$C_{12}H_{15}N_3O$	54.32 [c]	4.87 [c]	24.27 [c]	54.40 [c]	4.82 [c]	24.67 [c]
5b	40	102-103 [c]	$CHCl_3$	$C_{14}H_{19}N_3O$	56.57 [c]	5.51 [c]	23.38 [c]	56.60 [c]	5.46 [c]	23.10 [c]
5c	51	99-100	MeOH	$C_{22}H_{19}N_3O$	77.11	5.63	12.09	77.40	5.61	12.31
6a	20	108-109	MeOH	$C_{19}H_{20}N_6O$	65.49	5.82	24.19	65.50	5.79	24.12
7	21	97-98 [c]	$CHCl_3$	$C_{13}H_{17}N_3O$	55.50 [c]	5.13 [c]	23.89 [c]	55.60 [c]	4.91 [c]	23.89 [c]
8	25	110-111 [c]	$CHCl_3$	$C_{13}H_{17}N_3O$	55.55 [c]	5.13 [c]	23.95 [c]	55.60 [c]	4.91 [c]	23.89 [c]
14a	60	93-94	AcOEt	$C_{12}H_{13}N_3O_2$	62.13	5.64	18.02	62.33	5.67	18.17
14b	56	118	AcOEt/C_6H_{12}	$C_{22}H_{17}N_3O_2$	74.13	4.78	11.77	74.37	4.79	11.83
14c	56	84	AcOEt/C_6H_{12}	$C_{17}H_{15}N_3O_2$	69.60	5.14	14.27	69.61	5.15	14.33

[a] The solvent used for recrystallization of the analytical sample. [b] Isolated from a mixture of **3a** and **4a**. [c] The data for 2,4-dinitrophenylhydrazone derivatives. [d] HRMS found 362.1846, calcd. 362.1855.

Table 2

^1H NMR Spectral Data [a] for Mannich Derivatives of Carbonyl Compounds **3-8**, **14** and **15**

No.	Benzotriazolyl H-4	Benzotriazolyl H-5	Benzotriazolyl H-6	Benzotriazolyl H-7	H_α	H_β	Other
3a	8.01 (d, 8.3)	7.35 (dd, 6.9, 8.3)	7.49 (dd, 6.9, 8.3)	7.62 (d, 8.4)	4.87 (t, 6.0)	3.31 (t, 6.0)	1.07 (s, 9 H)
3b	7.97 (d, 8.4)	7.34 (dd, 6.7, 8.4)	7.49 (dd, 6.7, 8.3)	7.67 (d, 8.3)	4.99 (t, 6.0)	3.74 (t, 6.0)	7.38-7.49 (m, 3 H), 7.86 (d, 7.1, 2 H)
4a	8.05 (d, 8.4)	7.39 (dd, 6.6, 8.4)	7.49 [b]	7.49 [b]	4.76 (dd, 6.0,14.4), 4.98 (dd, 7.8,14.4)	4.59 (m)	0.67 (s, 9 H)
5a	8.02 (d, 8.4)	7.34 (dd, 6.9, 8.4)	7.48 (dd, 6.9, 7.9)	7.58 (d, 8.4)	4.55 (dd, 6.2,13.9), 4.89 (dd, 8.0,13.9)	3.50 (m)	0.94 (t, 7.2, 3 H), 1.21 (d, 7.2, 3 H), 2.31 (dq, 18.1, 7.2,1 H), 2.55 (dq, 18.1, 7.3, 1 H)
5b	8.01 (d, 8.4)	7.34 (dd, 6.8, 8.3)	7.46 (dd, 6.8, 7.8)	7.57 (d, 8.4)	4.59 (dd, 5.4,13.9), 4.86 (dd, 9.0, 13.9)	3.43 (m)	0.72 (t, 7.3, 3 H), 0.99 (t, 7.3, 3 H), 1.41 (sextet, 7.3, 2 H), 1.69 (m, 2 H), 2.22 (dt, 17.4, 7.0, 1 H), 2.40 (dt, 17.5, 7.4, 1 H)
5c	7.95 (d, 8.2)	7.28 [b]	7.28 [b]	7.28 [b]	4.71 (m)	5.23 (m)	3.59 (d, 15.7, 1 H), 3.66 (d, 15.8, 1 H), 6.85(m, 2 H),7.16(m, 4 H),7.28(m, 4 H) [b]
6a [c]	8.01 [b]	7.30-7.58 [b]	7.30-7.58 [b]	7.30-7.58 [b]	4.41 (dd, 5.1, 13.9), 4.84 (dd, 9.1, 13.9),	3.65 (m)	0.84 (d, 7.3, 6 H)
	8.01 [b]	7.30-7.58 [b]	7.30-7.58 [b]	7.30-7.58 [b]	4.53 (dd, 6.8, 13.9), 4.73 (dd, 7.1, 14.0)	3.51 (m)	1.20 (d, 7.1, 6 H)
7	8.02 (d, 8.3)	7.35 (dd, 7.4, 8.2)	7.49 (dd, 6.9, 7.4)	7.63 (d, 8.3)	4.85 (t, 6.6)	3.22 (t, 6.6)	0.85 (d, 6.6, 6 H), 2.09 (heptet, 6.7, 1 H), 2.30 (d, 7.0, 2 H)
8	8.01 (d, 8.4)	7.35 (dd, 7.0, 8.3)	7.49 (dd, 6.8, 7.8)	7.59 (d, 8.4)	4.58 (dd, 3.7, 13.7), 4.91 (dd, 10.3, 13.6)	3.45 (m)	1.08 (d, 6.9, 3 H), 1.13 (d, 6.8, 3 H), 2.04 (s, 3 H), 2.16 (m, 1 H)
14a	8.07 [b]	7.43 [b]	7.59 [b]	7.95 (d, 8.4)	5.09 (d, 6.9)	4.94 (t, 7.0)	2.28 (s, 6 H)
14b	7.93 [b]	7.29 (dd, 6.0, 8.4)	7.42 [b]	7.69 (d, 8.5)	5.33 (d, 6.6)	6.32 (t, 6.6)	7.42 (m, 4 H), 7.53 (m, 2 H), 7.93 (m, 4 H) [b]
14c	7.98 [b]	7.33 (dd, 7.3, 8.3)	7.48 [b]	7.64 [b]	5.09 (dd, 6.9, 14.2), 5.25 (dd, 6.9, 14.2)	5.64 (t, 6.8)	2.19 (s, 3 H), 7.48 (m, 2 H) [b], 7.64 (m, 1 H) [b], 7.98 (m, 1 H) [b]
15	8.07 [b]	7.43 [b]	7.59 [b]	7.95 (d, 8.4)	5.67 (s)	-	2.28 (s, 6 H)

[a] Chemical shifts in ppm from TMS, coupling constants (in parentheses) in Hz. [b] The resonances are overlapped. [c] A mixture of two diastereomers. Data for the predominant diastereomer are on the first line.

α-carbon atoms, reaction occurs on both sides of the carbonyl group leading to a mixture of two monosubstituted products. Thus, 4-methyl-2-pentanone gave an almost equimolar mixture of the product **7** resulting from the attack on the methyl group and its isomer **8** resulting from an attack on the methylene group. Electrophilic attack of **2** on the more stable enol form of 4-methyl-2-pentanone would give **8**; evidently steric shielding of the methylene by the adjacent isopropyl group, and relatively free access to the methyl group, accounts for the product mix found. Mannich reactions generally initially involve attack of the immonium cation on the C-atom bearing the least number of H-atoms, but the products so obtained under kinetic control can undergo thermal transaminomethylation to thermodynamically more stable products with the aminomethyl group on the least substituted C-atom [6].

In preliminary investigations, the reactivities at the α-methylene and at the carbonyl group were tested of the compounds obtained. Under strongly acidic conditions, butyl nitrite [7] converted products **3b** and **5a** into oximes **9** and **12**, respectively (Scheme 2). Anhydrous hydrogen chloride appeared to be also a good catalyst for condensation of **3b** with benzaldehyde giving the benzylidene derivative **10**. Attempted basic catalysis of this reaction led to complex mixtures. Compound **3b** was converted into hydrazone **11** by phenylhydrazine. The carbonyl group of **5a** was converted into ketal **13** by methyl orthoformate.

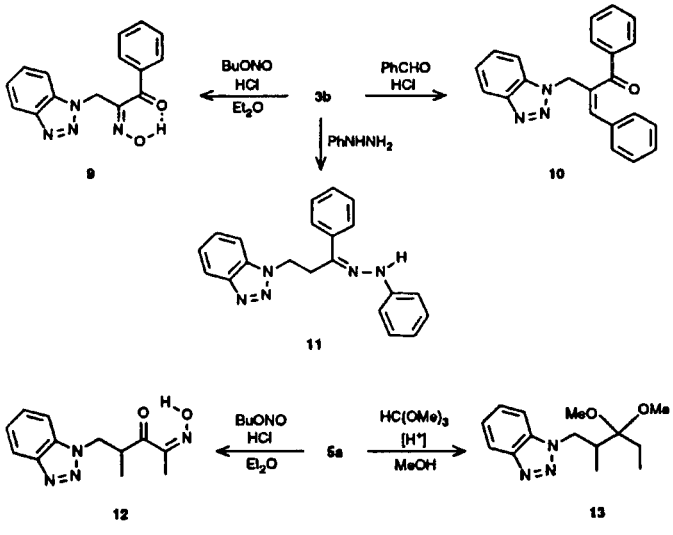
Table 3

^{13}C NMR Spectral Data [a] for Mannich Derivatives of Carbonyl Compounds **3-8, 14** and **15**

No.	Benzotriazolyl						C_α	C_β	C=O	Other4
	C-4	C-5	C-6	C-7	C-3a	C-7a4				
3a	119.5	123.7	127.2	109.6	145.5	133.0	42.6	36.2	212.6	25.8 (3 C), 44.0
3b	119.3	123.5	127.0	109.5	145.4	132.9	42.3	37.7	196.2	127.6 (2 C), 128.3 (2 C), 133.2, 135.6
4a	120.1	124.3	128.0	109.1	145.7	133.0	48.0	46.4	214.0	24.6 (3 C), 45.4
5a	119.5	123.7	127.2	109.5	145.4	133.0	49.1	45.6	211.9	7.2, 15.1, 34.8
5b	119.4	123.6	127.1	109.5	145.3	132.9	47.5	52.3	211.4	10.8, 13.1, 16.2, 22.9, 44.9
5c	119.6	123.7	127.2	109.6	145.4	133.2	49.4	57.3	205.2	48.7, 127.1, 128.4 (2 C), 128.5 (2 C), 128.6, 129.3 (2 C),129.4 (2 C), 132.9, 134.6
6a [b]	119.6	123.9	127.4	109.6	145.3	133.1	48.5	45.2	211.9	14.3
	119.7	123.9	127.5	109.3	145.5	132.9	49.4	45.6	212.7	14.9
7	119.6	124.0	127.4	109.7	145.5	133.1	42.1	52.0	207.2	22.3 (2 C), 24.4, 42.1
8	119.7	124.0	127.4	109.8	145.5	133.2	46.0	58.1	209.6	19.3, 20.6, 29.1, 31.3
14a	119.1	124.1	127.4	110.9	145.0	133.0	65.5	45.0	202.0	30.2
14b	119.6	124.0	127.7	110.0	145.5	133.4	46.3	56.5	193.5	128.6 (4 C), 129.0 (4 C), 134.1 (2 C), 135.1 (2 C)
14c	119.7	124.0	127.7	109.8	145.6	133.2	45.7	61.4	193.9 199.9	29.8, 128.8 (2C), 129.1 (2C), 134.4, 135.5
15	119.2	124.0	127.4	110.5	145.1	132.8	45.2	106.3	193.4	23.4

[a] Chemical shifts in ppm, with the $CDCl_3$ signal (δ 77.0) as a reference.[b] A mixture of two diastereomers. Data for the predominant diastereomer are on the first line.

Scheme 2

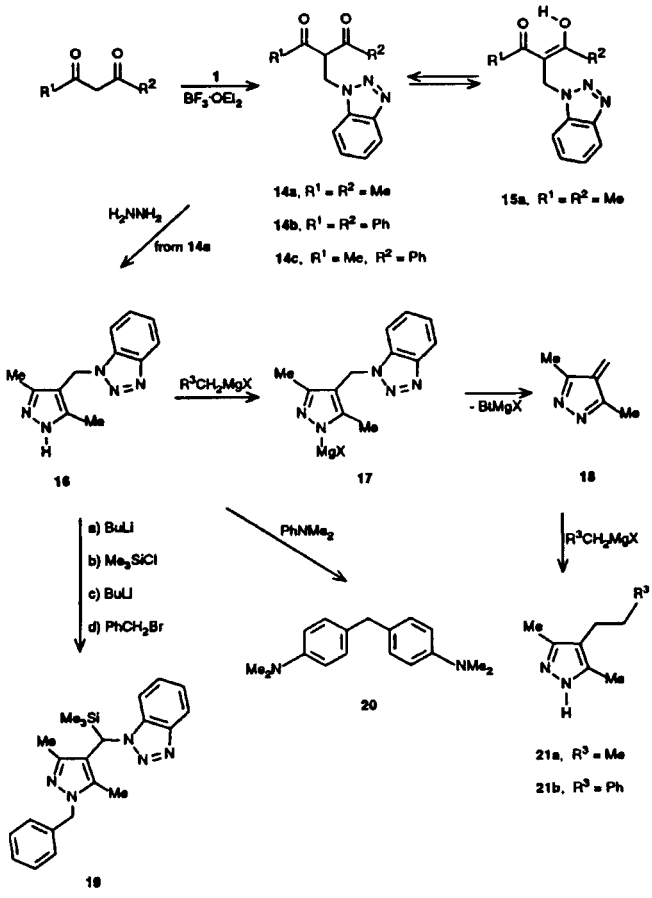


1,3-Diketones.

Reactions of **1** with 1,3-diketones (acetylacetone, dibenzoylmethane and acetylacetophenone) proceeded similarly to those with monoketones giving the corresponding monobenzotriazolylmethylated products **14** (Scheme 3). Although the nucleophilicity of the enol forms of these diketones is low, their concentration is high which compensates for their lowered reactivity. Compounds **14** were expected to be in equilibrium with their tautomeric enol forms **15**; although, **14a** exists as 67% of the keto form and 33% of the enol form **15a** in chloroform solution, no enol forms of **14b** and **14c** were detected in their nmr spectra (Tables 2 and 3).

A characteristic reaction of 1,3-dicarbonyl compounds is their condensation with hydrazine giving pyrazoles

Scheme 3



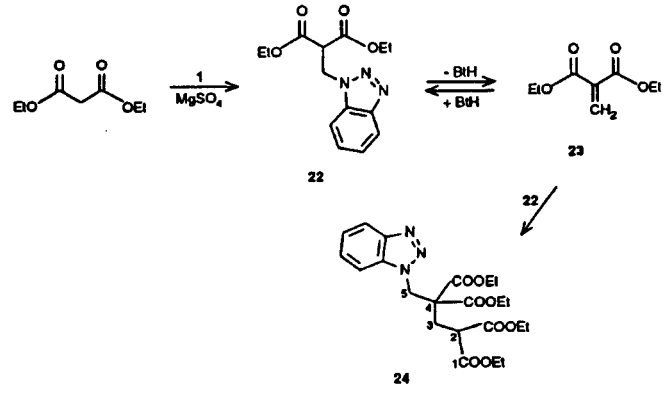
[8,9]. Diketone **14a** was thus converted quantitatively to pyrazole **16** in diethyl ether at 20°. We attempted to benzylate the methylene group in **16** by successive treatment with butyllithium, trimethylchlorosilane, butyllithium, and benzyl bromide. Unexpectedly, the 1-benzyl-4-[(benzotriazol-1-yl)-trimethylsilyl]methyl derivative **19** resulted. Evidently, the *N*-trimethylsilyl protective group introduced in the first step migrated to the methylene group upon treatment of the intermediate with the second mole of butyllithium. bis-(4-Dimethylaminophenyl)methane (**20**) was formed by reaction of **16** with *N,N*-dimethylaniline: presumably substitution of the benzotriazolyl moiety with the 4-(dimethylamino)phenyl group is followed by C-C bond cleavage.

The benzotriazolyl moiety in **16** can be substituted by an alkyl or aryl group from a Grignard reagent leading to 4-substituted pyrazoles **21**. In this case, the mechanism involves elimination from the magnesium complex **17** giving magnesium benzotriazolide and the methylidene derivative **18** which is then trapped by the Grignard reagent. The reaction was slow in refluxing THF; after 48 hours, substantial amounts of the starting materials were still present in the reaction mixture giving rise to moderate yields of products **21**. Work is envisaged to exploit this potentially convenient synthetic access to 4-substituted pyrazoles.

Diethyl Malonate.

Condensation of diethyl malonate with **1** proceeded in DMSO in the presence of anhydrous magnesium sulfate to give a mixture shown by nmr to be **22** and **24** from which pure **24** was separated in 64% yield by column chromatography. Formation of **24** can be explained by the elimination of benzotriazole from **22** with the formation of the methylidene derivative **23** to which then adds another molecule of **22**.

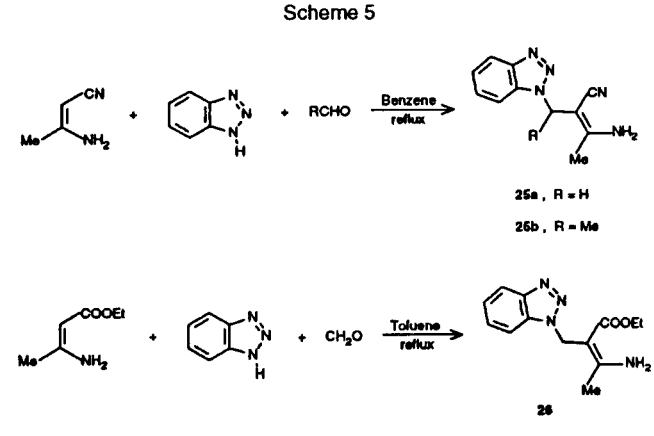
Scheme 4



Stabilized Enamines.

Electron densities on α-carbon atoms of β-aminocrotononitrile and ethyl β-aminocrotonate are sufficient for their direct condensation with **1** (formed *in situ* from benzotriazole and formaldehyde) without an added catalyst on refluxing in benzene or toluene with azeotropic removal of water. In this way, compounds **25a** and **26** were obtained in high yields (Scheme 5). The reaction with β-aminocrotononitrile, benzotriazole and acetaldehyde gave derivative **25b** in 72% yield.

Scheme 5



EXPERIMENTAL

Melting points (°) were determined with a hot-stage microscope and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Varian VXR-300 spectrometer using deuteriochloroform as the solvent and tetramethylsilane as the reference. All reagents were commercially available.

N-(Benzotriazol-1-yl)ketones **3-8,14** and **15**. General Procedure.

Boron trifluoride etherate (3.70 ml, 30 mmoles) was slowly added to a mixture of benzotriazole (1.19 g, 20 mmoles), paraformaldehyde (0.6 g, 20 mmoles) and the appropriate ketone (20 mmoles) and stirred under nitrogen at 23°. The resulting brown, viscous mixture was heated at 100° for 8 hours. After cooling, chloroform (10 ml) was added, the mixture was diluted with water and neutralized with aqueous 10% ammonium hydroxide. The chloroform layer was separated and the aqueous layer extracted with chloroform (3 x 10 ml). The combined extracts were washed with water (2 x 10 ml), brine (1 x 10 ml) and dried (magnesium sulfate). The solvent was removed and the residue was subjected to column chromatography (silica gel). Ketones **3-6** were eluted with chloroform, isomeric ketones **7** and **8** with a mixture of toluene/ethyl acetate (1:5) and ketone **14a** with a mixture of hexane/ethyl acetate (1:1). The oily substances were characterized as 2,4-dinitrophenylhydrazones. Compound **4a** was prepared in a similar manner but using 30 mmoles of benzotriazole and only 10 mmoles of ketone.

3-(Benzotriazol-1-yl)-2-(hydroxyimino)-1-phenylpropanone (**9**).

Hydrogen chloride gas was passed through the suspension of 3-(benzotriazol-1-yl)propiophenone (**3b**) (0.6 g, 2.4 mmoles) in *n*-butyl nitrite (0.26 g, 2.5 mmoles) and dry diethyl ether (10 ml) for 15 minutes at 25-30°. The reaction mixture was stirred for two days at 20° and the resulting solid was filtered off and recrystallized from ethanol to give **9** (0.4 g, 60%) as colorless prisms, mp 168-169°; ^1H nmr: 5.95 (s, 2 H), 7.39 (m, 2 H), 7.51 (m, 2 H), 7.62 (dd, J = 7.8 and 8.4 Hz, 1 H), 7.91 (m, 3 H), 8.03 (d, J = 8.5, 1 H), 12.45 (bs, 1 H); ^{13}C nmr: 40.7, 111.3, 118.3, 126.4, 128.3 (2 C), 129.0, 130.8 (2 C), 133.3, 133.7, 136.3, 142.2, 150.6, 190.4 (C=O).

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.31; H, 4.37; N, 20.05.

3-(Benzotriazol-1-yl)-2-benzylidenepropiophenone (**10**).

A mixture of 3-(benzotriazol-1-yl)propiophenone (**3b**) (0.5 g, 2 mmoles) and benzaldehyde (0.21 g, 2 mmoles) was treated with dry hydrogen chloride for 10 minutes and then heated at 50-55° for 2 days. After cooling, chloroform (10 ml) was added, the mixture was diluted with water and neutralized with cold aqueous 10% sodium hydroxide. The chloroform layer was separated and the aqueous layer further extracted with chloroform (2 x 10 ml). The combined extracts were washed with water (2 x 10 ml) and dried (magnesium sulfate). The solvent was evaporated and the resulting oil was purified by column chromatography using silica gel and chloroform as the eluent to give **10** (0.3 g, 50%) as an oil; ^1H nmr: 5.79 (s, 2 H), 7.43 (m, 8 H), 7.76 (m, 6 H), 8.02 (dd, J = 7.5 and 8.4 Hz, 1 H); ^{13}C nmr: 44.5, 110.1, 119.7, 123.9, 127.5, 128.3 (2 C), 128.9 (2 C), 129.3 (2 C), 129.6, 129.8 (2 C), 132.5, 133.5, 133.9, 134.5, 137.3, 145.6, 146.1, 197.0 (C=O).

Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 78.02; H, 5.19; N, 12.05.

3-(Benzotriazol-1-yl)propiophenone Phenylhydrazone (**11**).

A mixture of 3-(benzotriazol-1-yl)propiophenone (**3b**) (2.51 g, 10 mmoles), phenylhydrazine (1.08 g, 10 mmoles) and acetic acid (1.2 g, 20 mmoles) in methanol (30 ml) was stirred for one day at 20°. The resulting solid was filtered off, washed with water and dried to give **11** (3.0 g, 88%) as a colorless solid, mp 115-116°; ^1H nmr: 3.50 (t, J = 6.8 Hz, 2 H), 4.78 (t, J = 6.8 Hz, 2 H), 6.84 (dd, J = 6.4 and 7.4 Hz, 1H), 7.15 (d, J = 8.6 Hz, 2H), 7.28 (m, 8H), 7.72 (d, J = 8.1 Hz, 2H),7.93 (d, J = 8.4 Hz, 1 H); ^{13}C nmr: 25.7, 43.9, 108.9, 113.3 (2 C), 119.8, 120.3, 124.2, 125.1 (2 C), 127.6, 128.1, 128.5 (2 C), 129.0 (2 C), 133.0, 137.2, 139.4, 144.8, 145.6.

Anal. Calcd. for $C_{21}H_{19}N_5$: C, 73.86; H, 5.61; N, 20.52. Found: C, 73.86; H, 5.63; N, 20.65.

1-(Benzotriazol-1-yl)-4-(hydroxyimino)-2-methyl-3-pentanone (**12**).

Similarly to **9**, this compound was obtained from 1-(benzotriazol-1-yl)-2-methyl-3-pentanone (**5a**) (1.0 g, 4.6 mmoles) and *n*-butyl nitrite (0.48 g, 4.7 mmoles) in diethyl ether, in the presence of hydrogen chloride; colorless prisms (0.5 g, 45 %), mp 108°; ^1H nmr: 1.20 (d, J = 7.1 Hz, 3 H), 1.90 (s, 3 H), 4.46 (m, 1 H), 4.66 (dd, J = 6.6 and 13.9 Hz, 1 H), 4.92 (dd, J = 7.8 and 13.9 Hz, 1 H), 7.36 (ddd, J = 1.0, 7.3 and 8.3 Hz, 1 H), 7.48 (ddd, J = 1.0, 7.3 and 8.4 Hz, 1 H), 7.59 (dt, J = 1.0 and 8.4 Hz, 1 H), 8.01 (dt, J = 1.0 and 8.4 Hz, 1 H), 10.05 (bs, 1 H); ^{13}C nmr: 8.2, 15.8, 40.6, 50.0, 109.9, 119.6, 124.2, 127.5, 133.4, 145.2, 155.4 (C=N), 200.0 (C=O).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.59, H, 5.75; H, 22.65.

1-(Benzotriazol-1-yl)-3,3-dimethoxy-2-methylpentane (**13**).

A solution of 1-(benzotriazol-1-yl)-2-methyl-3-pentanone (**5a**) (1.75 g, 8 mmoles), trimethyl orthoformate (1.1 g, 10.4 mmoles) and *p*-toluenesulfonic acid (0.01 g, 0.008 mmole) in methanol (5 ml) was set aside for 48 hours and then neutralized with aqueous 5% sodium carbonate and filtered. The solvent was evaporated to give **13** (1.69 g, 80%) as an oil; ^1H nmr: 0.93 (d, J = 7.0 Hz, 3 H), 1.00 (t, J = 7.0 Hz, 3 H), 1.81 (m, 2 H), 2.55 (m, 1 H), 3.21 (s, 3 H), 3.34 (s, 3 H), 4.52 (dd, J = 10.8 and 13.7 Hz, 1 H), 4.98 (dd, J = 11.0 and 13.7 Hz, 1 H), 7.35 (m, 1 H), 7.48 (m, 1 H), 7.60 (d, J = 8.4 Hz, 1 H), 8.05 (d, J = 8.4 Hz, 1 H); ^{13}C nmr: 8.5, 13.2, 24.8, 39.7, 48.1, 49.04, 50.4, 103.1, 109.5, 119.8, 123.6, 126.9, 132.8, 145.9; hrms: Calcd. for $C_{14}H_{22}N_3O_2$: 264.1712. Found: 264.1717.

4-(Benzotriazol-1-ylmethyl)-3,5-dimethyl-1,2-pyrazole (**16**).

A mixture of 3-(benzotriazol-1-ylmethyl)-2,4-pentanedione (**14a**) (0.7 g, 3.0 mmoles) and hydrazine hydrate (0.1 ml, 3.0 mmoles) in diethyl ether (20 ml) was stirred for 2 days at 20° and then the solvent was evaporated *in vacuo* to give **16** (0.68 g, 100%) as a colorless solid, mp 174°. ^1H nmr: 2.25 (s, 6 H), 5.62 (s, 2 H), 7.34 (m, 3 H), 8.01 (dt, J = 1.1 and 7.8 Hz, 1 H); ^{13}C nmr: 10.7 (2 C), 42.1, 108.8, 109.4, 119.5, 123.6, 127.0, 132.2, 143.1 (2 C), 145.8.

Anal. Calcd. for $C_{12}H_{13}N_5$: C, 63.42; H, 5.77; N, 30.82. Found: C, 63.12; H, 5.79; N, 30.50.

1-Benzyl-4-[(benzotriazol-1-yl)-trimethylsilyl]methyl-3,5-dimethylpyrazole (**19**).

To a solution of 4-(benzotriazol-1-ylmethyl)-3,5-dimethylpyrazole (**16**) (1.0 g, 4.4 mmoles) in dry THF (20 ml) was added butyllithium (1.76 ml, 4.4 mmoles, 2.5 *M* in *n*-hexane) under nitrogen at -78°. After stirring the reaction mixture for 15 minutes at -78°, trimethylchlorosilane (0.48 g, 4.4 mmoles) was added and after further stirring for 15 minutes, butyllithium (1.76 ml, 4.4 mmoles, 2.5 *M* in *n*-hexane) was added dropwise to the mixture, still at -78°. The stirring was continued for 30 minutes at -78° and benzyl bromide (0.75 g, 4.4 mmoles) in THF (3 ml) was added dropwise at -78°. After being warmed to room temperature, the mixture was stirred for another 6 hours, poured into ice-water (50 ml), extracted with diethyl ether (3 x 20 ml), washed with water (2 x 10 ml) and dried (magnesium sulfate). After removal of the solvent, the light brown residue was subjected to column chromatography (silica gel/chloroform) to give **19** (1.0 g, 60%) as an oil; ^{1}H nmr: 0.32 (s, 9 H), 1.70 (s, 3 H), 2.08 (s, 3 H), 5.09 (s, 1 H), 5.16 (s, 2 H), 6.84 (m, 2 H), 7.07-7.10 (m, 1 H), 7.20-7.39 (m, 5 H), 8.01 (m, 1 H); ^{13}C nmr: -1.5 (3 C), 9.9, 12.3, 47.3, 52.7, 110.2, 113.4, 119.9, 123.8, 126.0 (2 C), 126.7, 127.4, 128.6 (2 C), 133.6, 136.3, 137.0, 145.2, 145.9.

Anal. Calcd. for $C_{22}H_{27}N_5Si$: C, 67.83; H, 6.99; N, 17.98. Found; C, 68.19; H, 6.79; N, 17.59.

Bis-(4-dimethylaminophenyl)methane (**20**).

A mixture of 4-(benzotriazol-1-ylmethyl)-3,5-dimethylpyrazole (**16**) (1.12 g, 5 mmoles) and *N,N*-dimethylaniline (0.6 g, 5 mmoles) was stirred under nitrogen at 140-160° for 30 hours and then dissolved in chloroform (15 ml). The chloroform solution was poured into ice-water (50 ml) and the layers were separated. The aqueous layer was extracted with chloroform (3 x 10 ml), the combined organic extracts were washed with aqueous 10% sodium carbonate (1 x 10 ml), water (3 x 10 ml) and dried (magnesium sulfate). The solvent was evaporated and the residue was subjected to column chromatography using silica gel and toluene/ethyl acetate (4:1) as the eluent to give **20** (0.4 g, 64%) as a colorless solid, mp 87-88° (lit [10] mp 88-89°.

3,5-Dimethyl-4-propylpyrazole (**21a**).

To a stirred solution of 4-(benzotriazol-1-ylmethyl)-3,5-dimethylpyrazole (**16**) (1.12 g, 5 mmoles) in dry THF (15 ml) and toluene (15 ml) was added ethylmagnesium bromide (5 ml, 15 mmoles, 3 *M* in diethyl ether) at 20°. Diethyl ether was distilled off and the resulted solution was refluxed for two days. The reaction mixture was poured into ice-water (50 ml) and extracted with diethyl ether (3 x 10 ml). The combined extracts were washed with aqueous 10% sodium carbonate (1 x 10 ml) followed by water (3 x 10 ml) and dried (magnesium sulfate). The solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (silica gel/toluene/ethyl acetate 1:1) to give **21a** (0.3 g, 45%) as a colorless solid, mp 77-78° (lit [11] mp 77.5-78.5°); ^{1}H nmr: 0.89 (t, J = 7.3 Hz, 3 H), 1.46 (sextet, J = 7.3 Hz, 2 H), 2.20 (s, 6 H), 2.31 (t, J = 7.4 Hz, 2 H); ^{13}C nmr: 10.8, 13.7 (2 C), 23.7, 25.0, 115.3, 141.8 (2 C).

3,5-Dimethyl-4-(phenylethyl)pyrazole (**21b**).

Similarly to **21a**, this compound was prepared from 4-(benzotriazol-1-ylmethyl)-3,5-dimethylpyrazole (**16**) (0.78 g, 3 mmoles) and benzylmagnesium chloride (10.8 ml, 15 mmoles, 1.2 *M* in diethyl ether) refluxed in THF (40 ml) for 12 hours; colorless solid (0.3 g, 50%), mp 92-93°; ^{1}H nmr: 2.04 (s, 6 H), 2.63 (m, 2 H), 2.70 (m, 2 H), 7.07 (m, 2 H), 7.22 (m, 3 H), 8.67 (bs, 1 H); ^{13}C nmr: 10.5 (2 C), 25.3, 36.9, 114.4, 125.8, 128.2 (2 C), 128.6 (2 C), 141.8 (2 C), 142.1.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.95; H, 8.06; N, 13.99. Found: C, 78.05; H, 7.96; N, 13.92.

Ethyl 5-(Benzotriazol-l-yl)-2,4,4-tricarbethoxypentanoate (**24**).

A mixture of ethyl malonate (1.60 g, 10 mmoles), 1-(hydroxymethyl)benzotriazole (1.49 g, 10 mmoles), magnesium sulfate (0.24 g, 20 mmoles) and DMSO (3 ml) was stirred under nitrogen at 70° for 7 hours and poured into ice-water (50 ml). Extraction with diethyl ether (2 x 30 ml), washing of the combined extracts with water, drying over magnesium sulfate and evaporation of the solvent gave an oil which was subjected to column chromatography using silica gel and benzene/chloroform/dioxane (20:20:1) as the eluent. The first fraction (0.05 g) appeared to be diester **22** slightly contaminated with **24**. The second fraction gave tetraester **24** (1.47 g, 64%) as an oil: ^{1}H nmr: 1.20 (t, J = 7.2 Hz. 6 H). 1.24 (t, J = 7.1 Hz, 6 H), 2.62 (d, J = 6.2 Hz, 2 H), 3.85 (t, J = 6.2 Hz, 1 H), 4.15 (m, 8 H), 5.19 (s, 2 H), 7.36 (m, 1 H), 7.50 (m, 1 H), 7.58 (d, J = 8.3 Hz, 2 H), 8.03 (d, J = 8.3 Hz, 1 H); ^{13}C nmr: 13.7 (2 C, Et), 13.9 (2 C, Et), 30.4 (C-3), 48.3 (C-2), 50.2 (C-5), 57.4 (C-4), 61.7 (2 C, Et), 62.4 (2 C, Et), 109.6 (Bt), 120.0 (Bt), 124.0 (Bt), 127.7 (Bt), 133.8 (Bt), 145.5 (Bt), 168.8 (4 C, C=O).

Anal. Calcd. for $C_{22}H_{29}N_3O_8$: C, 57.01; H, 6.31; N, 9.07. Found: C, 56.91; H, 6.35; N, 9.03.

3-Amino-2-(benzotriazol-1-ylmethyl)crotononitrile (**25a**).

3-Aminocrotononitrile (1.64 g, 20 mmoles), benzotriazole (3.0 g, 25 mmoles) and 37% formaldehyde (2.2 ml, 25 mmoles) were refluxed in benzene (80 ml) for 8 hours. Water was collected in a Dean-Stark trap. The solvent was evaporated in *vacuo* and the resulting oil was purified by column chromatography on silica gel with hexane/ethyl acetate (1:1) as the eluent to give **25a** (4.0 g, 94%) as a colorless solid, mp 127-128°; ^{1}H nmr: 2.09 (s, 3 H), 5.34 (s, 2 H), 6.08 (bs, 2 H), 7.40 (dd, J = 8.0 and 15.4 Hz, 1 H), 7.52 (dd, J = 7.8 and 15.1 Hz, 1 H), 7.78 (d, J = 8.4 Hz, 1 H), 8.01 (d, J = 8.4 Hz, 1 H); ^{13}C nmr: 20.2, 45.7, 70.3, 109.9, 119.2, 122.4, 123.9, 127.4, 131.9, 145.6, 161.1.

Anal. Calcd. for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84. Found: C, 62.05; H, 5.21; N, 33.17.

3-Amino-2-(1-benzotriazol-1-ylethyl)crotononitrile (**25b**).

Similarly to **25a**, this compound was obtained from 3-aminocrotononitrile (1.64 g, 20 mmoles), benzotriazole (2.4 g, 20 mmoles) and acetaldehyde (1.1 g, 25 mmoles) refluxed in benzene (80 ml); colorless solid (3.27 g, 72%), mp 119-120°; ^{1}H nmr: 1.97 (d, J = 7.2 Hz, 3 H), 2.11 (s, 3 H), 5.22 (bs, 2 H), 5.90 (q, J = 7.2 Hz, 1 H), 7.38 (dd, J = 7.5 and 14.4 Hz, 1 H), 7.51 (dd, J = 7.1 and 15.4 Hz, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 8.02 (d, J = 7.9 Hz, 1 H); ^{13}C nmr: 18.8, 20.9, 53.2, 77.4, 111.2, 119.9, 120.6, 124.3, 127.7, 130.7, 146.8, 159.7.

Anal. Calcd. for $C_{12}H_{13}N_5$: C, 63.42; H, 5.77; N, 30.82. Found: C, 63.71; H, 5.80; N, 31.24.

Ethyl 3-Amino-2-(benzotriazol-1-ylmethyl)crotonate (**26**).

Similarly to **25a**, this compound was obtained from ethyl 3-aminocrotonate (2.60 g, 20 mmoles), benzotriazole (3.0 g, 25 mmoles) and 37% formaldehyde (2.2 ml, 25 mmoles) refluxed in toluene (80 ml); colorless solid, (3.1 g, 60%), mp 95-96°; ^{1}H nmr: 1.21 (t, J = 7.1 Hz, 3 H), 2.29 (s, 3 H), 4.17 (q, J = 7.1 Hz,

2 H), 5.33 (bs, 1 H), 5.50 (s, 2 H), 7.32 (dd, J = 6.1 and 13.5 Hz, 1 H), 7.42 (dd, J = 6.3 and 9.5 Hz, 1 H), 7.67 (d, J = 8.4 Hz, 1 H), 8.00 (d, J = 8.3 Hz, 1 H), 8.83 (bs, 1 H); ^{13}C nmr: 14.5, 21.2, 46.2, 59.3, 88.7, 110.7, 119.4, 123.4, 126.5, 132.8, 145.7, 162.8, 169.2 (C=O).

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 60.15; H, 6.21; N, 21.76.

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