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Reactivity of 4(7)-Aminobenzimidazole as a Bidentate Nucleophile.

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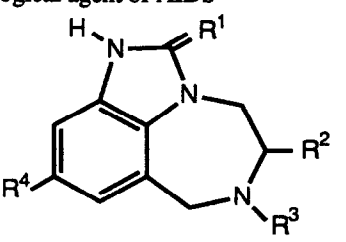
Key Words. *7H-Imidazo[1,5,4-e,f][1,5]benzodiazepin -4-ones, 4(7)-Amino- benzimidazole, Bidentate nucleophile, Nitrogen bridged heterocycles*

Abstract- *Reactivity of 4(7)-aminobenzimidazole as a bidentate nucleophile has been investigated 7-H-Imidazo [1,5,4-e,f][1,5] benzodiazepin-4-ones or imidazo [4,5-h] quinoline derivatives are obtained with β-oxoesters or β-diketones respectively*

It has been reported recently that several members of a novel series of 1*H*-tetrahydroimidazo[4,5,1-j,k][1,4]benzodiazepin-2-one and -thione derivatives (TIBO, I) inhibit the replication of HIV-1, the main aetiological agent of AIDS[1]



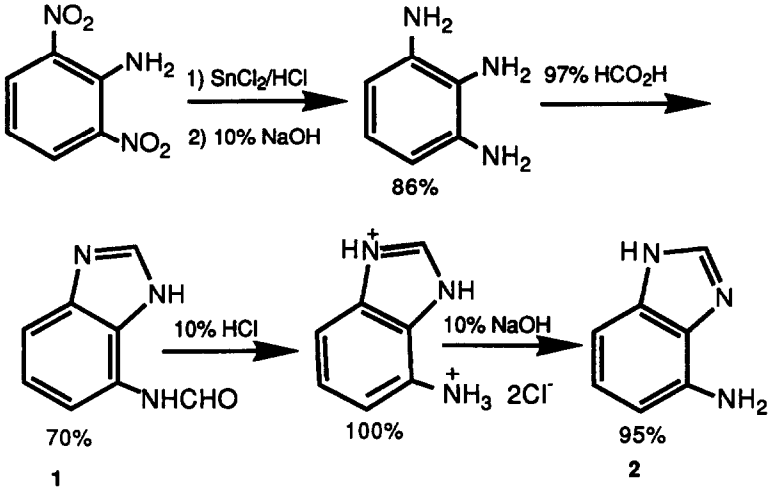
I R^1=S,O

In this paper we report the synthesis of imidazo[1,5,4-e,f][1,5]benzodiazepines, which can be considered analogues of I, by condensation of 4(7)-aminobenzimidazole (2) with β-dicarbonyl compounds, following a methodology previously studied for 1,2-diamino- benzimidazole[2-4]

Through reinvestigation of early reports based on Phillip´s benzimidazole synthesis[5] , in which several experimental details were absent[6,7], we have developed a reliable procedure for preparing 2 starting from commercial 2,6-dinitroaniline (Scheme 1).

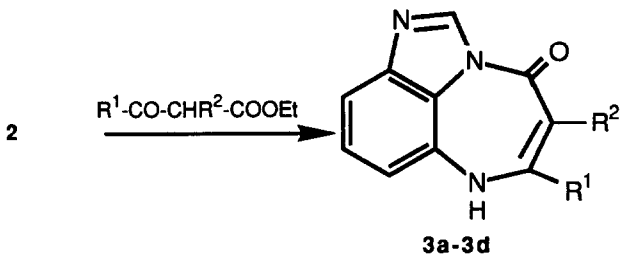
Alkylation reactions of 2 seem to be governed by steric effects and take place on the N^1-nitrogen atom preferentially[8], while acylation[9] and condensation reactions with aldehydes or

ketones[10] selectively occur on the amino group. However, as far as we know, no experimental data about the reactivity of **2** as a bidentate nucleophile have been reported.



Scheme 1

Uncatalyzed reactions of **2** with equimolar amounts of β-oxoesters were regioselective, affording 7*H*-imidazo[1,5,4-e,f][1,5]benzodiazepin-4-ones (**3**) in about 50% yield (Scheme 2). The products were easily separated from the starting **2** Only in the case of ethyl 2-oxo-cyclohexanecarboxylate, could traces of the minor isomer **4d** be isolated and characterized

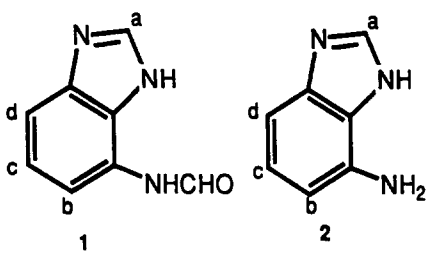


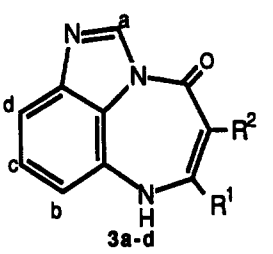
Compound	R^1	R^2	Yield %
3a	CH_3-	H-	68
3b	$CH_3CH_2CH_2$-	H-	33
3c	-$CH_2CH_2CH_2$-		60
3d	-$CH_2CH_2CH_2CH_2$-		40

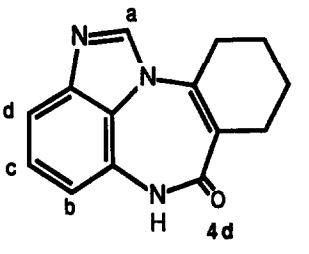
Scheme 2

The structural assignment of compounds **3** and **4d** was based on the chemical shift values of the benzimidazole protons (Table 1)

Table1 - ^{1}H-NMR chemical shifts (relative to TMS, DMSO-d_6).





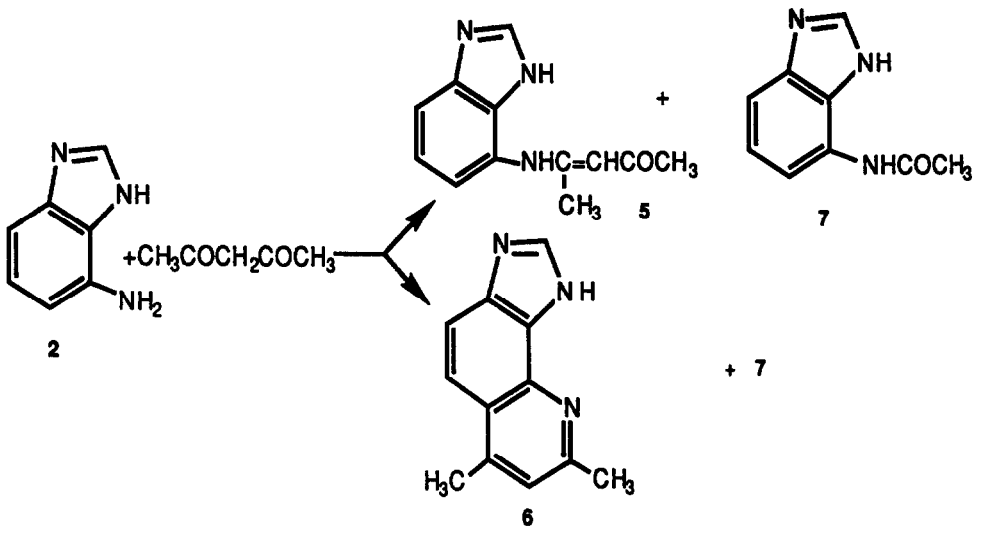


Compound	δ-Ha	δ-Hb	δ-Hc	δ-Hd	Other protons
1*	8 26 (s)	7.96 (d)	7.17 (t)	7.17 (t)	12.57 (s, 1H); 10.33 (d, 1H), 8.47 (d, 1H)
1**	8 28 (s)	6 92 (d)	7.31 (t)	7.31 (t)	12.57 (s, 1H), 10.25 (d, 1H); 9.69 (d, 1H)
2	7.80 (s)	6.65 (d)	6 30 (dd)	6.65 (d)	
3a	8 44 (s)	6.66 (d)	7 04 (t)	7 12 (d)	9 62 (s, 1H), 4.52 (s, 1H), 1.99 (s,3H)
3b	8 50 (s)	6 71 (d)	7 07 (t)	7.10 (d)	9.55 (s, 1H); 4.54(s, 1H); 2.17 (t, 2H), 1.63 (m, 2H); 0.97 (t, 3H)
3c	8 40 (s)	6 53 (d)	6 98 (t)	7 05 (d)	9.73 (s, 1H), 2.58 (m, 4H); 1 74 (m, 2H)
3d	8.45 (s)	6 59 (d)	6.98 (t)	7 02 (d)	8 93 (s, 1H); 2.32 (m, 4H); 1.56 (m, 4H)
4d	8 22 (s)	7 86 (d)	7 15 (t)	7 30 (d)	10 16 (s, 1H); 2.56 (t, 2H); 1.53 (t, 2H); 0.87 (m, 4H)

*cis- isomer; **trans- isomer

Two absorption patterns have been observed for Hb-Hd protons In one of them, corresponding to compounds **2** and **3**, the chemical shifts of Hb protons, according to their nature of protons *ortho* to an "aniline" moiety, appear at δ= 6.5-6.7 ppm In the other, corresponding to compounds **1** and **4d**, said proton is strongly deshielded to δ= 6 9-8 0 ppm, according to the weaker electron-donor effect of the *ortho* "amide" substituent. The chemical shift values found for Ha protons in compounds **3a-3d** are also in accordance with the anisotropic diamagnetic effect of the C_4=O carbonyl group The ^{1}H-NMR spectrum of compound **1** shows a 1.1 mixture of *cis*- and *trans*-isomers, clearly distinguished by the $J_{H,H}$ coupling constants found for the formamide substituent (1 59 Hz and 10 72 Hz respectively)

The reactions of **2** with acetylacetone in a molar ratio 1.5 gave compounds **5** (uncatalyzed reaction) or **6** (acid catalyzed) Compound **7** was obtained as secondary product in both experiments No traces of imidazo[1,5,4-e,f][1,5]benzodiazepines were observed (Scheme 3) The cyclization to **6** corresponds to a Combes synthesis for quinolines[11] The acetanilide **7** is formed by hydrolysis of **5.**



Scheme 3

EXPERIMENTAL

Melting points are uncorrected and were measured with a Büchi capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer and NMR spectra with a Varian VXR-300 (300 MHz) spectrometer (shifts in ppm relative to TMS). Microanalyses were performed with a Perkin-Elmer 2400 CHN analyzer

Preparation of 4(7)-formylbenzimidazole (1)

A mixture of 1 0 g (5.5 mmol) of 2,6-dinitroaniline, 11.08 g (49.2 mmol) of tin (II) chloride dihydrate and 16 4 ml of hydrochloric acid, was refluxed with stirring for 5 h. After cooling to room temperature, 0 92 g (86%) of bis 1,2,3-triaminobenzene hydrochloride were collected by filtration as colorless needles mp >300° (lit.[12] >300°C) After dissolving this compound in 10% NaOH (5 ml) and evaporating to dryness under reduced pressure, the residual solid was extracted with ethyl acetate (50 ml) After evaporation of the solvent at reduced pressure, 0.57 g (98%) of 1,2,3-triaminebenzene as free base, were obtained mp 102-103°C (lit.[12] 103-104°C). 0.57 g (4.6 mmol) of 1,2,3-triaminobenzene were refluxed for 1 h with 2.3 ml of 97% formic acid. The tea-colored solution thus obtained, was evaporated almost to dryness under reduced pressure, dissolved with heating in 2 9 ml of water and neutralized with ammonia After cooling, the precipitate was filtered and recrystallized from water with charcoal to give 0 62 g (70%) of **1**· mp· 173-175°C (lit.[7] 172-174° C)

Hydrolysis of 1 to 2.

A solution of 0 52 g (3 2 mmol) of **1** in 12.2 ml of 10% hydrocloric acid was refluxed with stirring for 30 min After evaporation to dryness at reduced pressure, 0.65 g (99%) of bis 4(7)-aminobenzimidazole hydrochloride were obtained. After dissolving in 10% NaOH (3 ml), the concentrated solution afforded a solid, which was extracted with absolute ethanol. Evaporation of the solvent at reduced pressure gave 0 41g (99%) of **2** as an oil, which was used without further purification An analytical sample obtained by distillation had mp: 120-121°C (lit.[13] 120-121°C).

Reactions of 4(7)-aminobenzimidazole with β-ketoesters to furnish compounds 3 (and 4d)·

Equimolecular amounts of 4(7)-aminobenzimidazole and β-ketoester were refluxed with stirring for 2 h. The obtained mixture was cooled and filtered and the solid was purified by chromatography on silica gel.

6-Methyl-7*H*-imidazo[1,5,4-e,f][1 5]benzodiazepin-4-one (**3a**) mp. >300°C (petroleum ether/ethyl acetate, 1 1), ν (KBr) 1670 cm^{-1} (C=O) Anal Calcd for $C_{11}H_9N_3O$ C, 66.33, H, 4.52, N, 21 10. Found C, 65 96, H, 4 37; N, 21 10

6-Propyl-7*H*-imidazo[1,5,4-e,f][1,5]benzodiazepin-4-one (**3b**) mp: >300°C (petroleum ether/ethyl acetate, 1.1),ν (KBr) 1670 cm^{-1} (C=O) Anal Calcd. for $C_{13}H_{13}N_3O$. C, 68 72, H, 5 72, N, 18 50 Found C, 68 42, H, 5 82; N, 18.42

5,6-trimethylene-7*H*-imidazo[1,5,4-e,f][1,5]benzodiazepin-4-one (**3c**): mp: >300°C (chloroform), ν(KBr) 1660 cm^{-1} (C=O) Anal Calcd for $C_{13}H_{11}N_3O$: C, 69 33; H, 4.88, N, 18.50 Found C, 69 01, H, 4 83, N, 18 48

5,6-Tetramethylene-7*H*-imidazo[1,5,4-e,f][1,5]benzodiazepin-4-one (**3d**) mp: >300°C (ethyl ether/ethanol, 8 2), ν (KBr) 1640 cm^{-1}(C=O) Anal Calcd. for $C_{14}H_{13}N_3O$ C, 70 29, H, 5 44, N, 17 57 Found C, 69 64, H, 5 22, N, 17 72

4,5-Tetramethylene-7*H*-imidazo[1,5,4-e,f][1,5]benzodiazepin-6-one (**4d**). mp· 143- 145°C (ethyl ether/ethanol, 8 2), ν (KBr)· 1720 cm^{-1}(C=O) Anal Calcd for $C_{14}H_{13}N_3O$ C, 70 29; H, 5 43, N, 17 57 Found C, 69 99, H, 5 40, N, 17 60

Reactions of 4(7)-aminobenzimidazole with β-diketones.

a) A solution of 0 968 g (7 28 mmol) of **2** in 3.64 g (36 4 mmol) of acetylacetone was refluxed for 12 h with stirring The reaction mixture was purified by column chromatography (silica gel) using EtOAc/EtOH (9 1) as eluent to give 0 31 g (20 %) of **5** and 0 14 g (11%) of **7**

4(7)(1-Methyl-3-oxo-1-butenyl)aminobenzimidazole (5) : mp: 105-106° C, ν (KBr): 1720 cm^{-1}(C=O). Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.98; H, 6.04; N, 19.53. Found: C. 66.85; H, 6.20, N, 19.20

4(7)-Acetamidobenzimidazole (7) : mp: 284-286° C, ν (KBr). 1650 cm^{-1} (C=O). Anal Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.38; H, 5.25; N, 23.69.

b)A solution of 0.97 g of 4(7)-aminobenzimidazole (7.3 mmol) and 0.72 g (7.3 mmol) of acetylacetone in 3 ml of glacial acetic acid was refluxed with stirring for 2 h. After cooling, the mixture of reaction products was separated by chromatography in silica gel using EtOAc/EtOH (9:1) as eluent to give 0 24 g (21%) of compound **6** and 0 15 g (11%) of compound **7.**

1*H*-6,8-Dimethyl-imidazo[4,5-h]quinoline (6): mp: 287-288°C. Anal Calcd. for $C_{12}H_{11}N_3$· C, 73 09, H, 5.58, N, 21 37. Found: C, 72.68; H, 5.62; N, 21.48.

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