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A New 1,2,3-Triazolo[1,2]benzodiazepine Ring System

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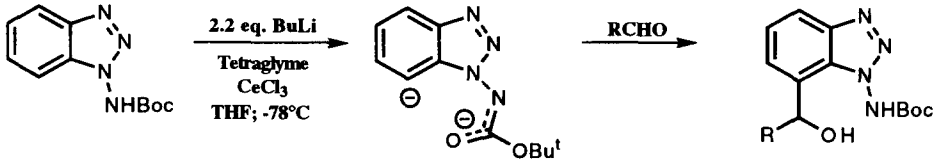
Abstract:- *Dianion **2** derived from N-Boc-aminobenzotriazole **1** condenses in a [1.2]-fashion with α,β-unsaturated aldehydes; subsequent oxidation of the resulting allylic alcohols **7** using manganese(IV) oxide or, less effectively, treatment of the derived acetates **10** with Pd(0), results in direct formation of the novel triazolo[1,2]-benzodiazepines **9** and **11** by intramolecular addition of the pendant amino group.*

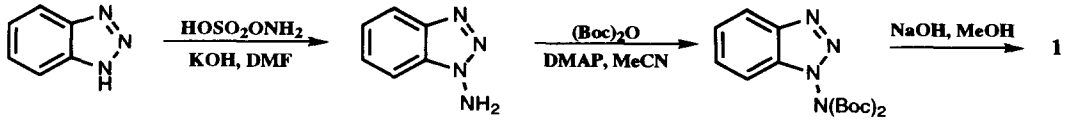
We have recently reported[1] that the dianion **2** can be smoothly generated from *N*-Boc-1-aminobenzotriazole **1**, by a lateral lithiation reaction,[2] promoted by the ionized *N*-Boc group; subsequent condensations with aldehydes and related electrophiles, in the presence of cerium(III) chloride, gave homologues **3** (Scheme 1). Such derivatives are useful as precursors to substituted benzynes which can be trapped intramolecularly by suitably positioned hydroxyl groups, resulting in novel approaches to dihydrobenzofurans, chromans and related *O*-heterocyclic systems.[3]



1 **2** **3**

Scheme 1

The starting material **1** is available from benzotriazole **4** *via* a three-step process consisting of initial *N*-amination using hydroxylamine-*O*-sulfonic acid;[3,4] during the present work, we have found that this step gives



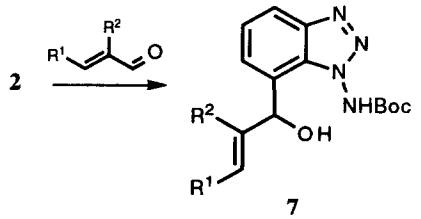
4 **5** **6**

Scheme 2

much higher yields when the reaction is carried out in dimethylformamide (Scheme 2).[5] Incorporation of the *N*-

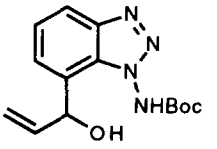
Boc protecting group was complicated by the high nucleophilicity of the *N*-amino group. All attempts to introduce a single Boc group failed and instead, only the *bis*-Boc derivative **6** could be isolated, along with starting material **5**, even when a deficiency of the acylating agent [typically Boc anhydride, $(Boc)_2O$)] was used, under a variety of conditions. Fortunately, partial hydrolysis of the *bis*-Boc derivative **6** was achievable in excellent yield by brief exposure to methanolic base.[3] We wondered if the high nucleophilicity inherent in this type of *N*-Boc function could perhaps be exploited, in combination with the dianion chemistry, to provide approaches to a variety of novel heterocyclic systems by intramolecular cyclisations. Herein, we report a successful realization of these ideas in approaches to a 1,2,3-triazolo[1,2]benzodiazepine ring system which, to the best of our knowledge, has not been previously reported.

Condensation of the dianion **2**, prepared under our previously reported conditions,[1] with α,β-unsaturated aldehydes proceeded smoothly in a [1,2]-fashion, attesting to the hardness of dianion **2**, to provide excellent yields of the allylic alcohols **7** (Scheme 3).[6] The parent member **8** of this series was obtained, in >90% isolated yield, in an alternative manner by the reaction of 7-formyl-1-(*N*-Boc-amino)benzotriazole[1] with 2.2 equivalents of vinylmagnesium bromide in tetrahydrofuran at -78°C for 5 min. We reasoned that a suitable oxidation method would lead to the corresponding unsaturated ketones which might undergo intramolecular Michael addition by the *N*-Boc function.



7

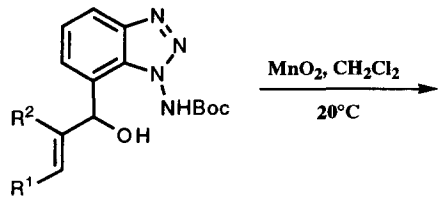
	R^1	R^2	Yield
a)	Me	H	92% (95%)
b)	n-Pr	H	87% (92%)
c)	Me	Me	89% (96%)
d)	Ph	H	71% (78%)
e)	2-Furyl	H	75% (85%)



8

Scheme 3

In the event, we were delighted to find that exposure of the parent member **8** to activated manganese dioxide[7] [3 g $mmol^{-1}$ of allylic alcohol] in dichloromethane at ambient temperature for 3h lead to an essentially quantitative yield of the [1,2]-benzodiazepin-7-one **9a** (Scheme 4). Full characterization data, together with an



7,8 9

	R^1	R^2	Time (h)	Yield
a)	H	H	3	95%
b)	Me	H	3	92%
c)	n-Pr	H	3	91%
d)	Me	Me	24	85%
e)	Ph	H	36 [Et_3N]	76%
f)	2-Furyl	H	36 [Et_3N]	78%

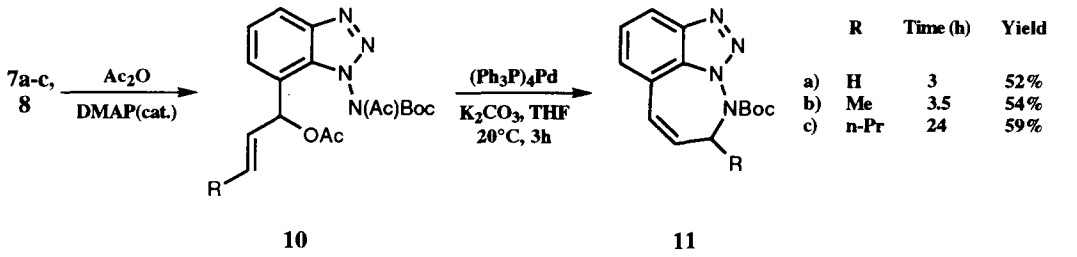
Scheme 4

X-ray crystallographic analysis,[6,8] have established the structure. An alkyl group at the β-position of the intermediate enone had little effect upon the rate of the Michael addition and the benzodiazepinones **9b,c** were

isolated in similarly excellent yields. Methyl groups at both the α- and β-positions did, as expected, slow the rate of the overall reaction but did not prevent the efficient formation of the 5,6-disubstituted derivative **9d** as a single diastereoisomer; a coupling constant of 10.0 Hz between the two methine protons indicated that this has the *trans* stereochemistry. β-Aryl groups did, however, inhibit the Michael addition under the conditions of the oxidation, which also occurred much more slowly with these substrates; fortunately, the intermediate enones underwent smooth cyclisation when exposed to triethylamine [20 mol%, CH_2Cl_2, 20°C, <1h] to give the expected products **9e,f**.

The ^1H NMR spectra of all the benzodiazepinones **9** in $CDCl_3$ at ambient temperature were complicated by extensive line broadening, presumably due either to rotation of the Boc function or to pseudorotation of the new seven-membered ring, where one methylene group is above the plane of the aromatic system and the other below. At higher temperatures [≥ 70°C], essentially first order spectra were observed.[9]

The availability of the allylic alcohols **7** and **8** also suggested an alternative method for effecting cyclisation using palladium-catalysed generation of a π-allyl complex from the corresponding acetates.[10] The success of the foregoing Michael additions suggested that the amino group would also be sufficiently nucleophilic to trap such intermediates. However, it turned out that the high nucleophilicity posed an immediate problem of selective acetylation, as expected from the foregoing preparation of the *bis-N*-Boc derivative **6** (Scheme 2). Treatment of the allylic alcohols **7**, and **8** with acetic anhydride and DMAP (cat.) in dichloromethane led to excellent yields of the corresponding *bis-N,O*-acetates **10**; all attempts to achieve selective *O*-acetylation were unsuccessful (Scheme 5).[11] However, exposure of the *bis*-acetates [**10**; R = H or n-alkyl] to a Pd(0) catalyst led to reasonable yields of the unsaturated [1,2]benzodiazepines **11**. Also isolated were smaller quantities (15~20%) of the corresponding free secondary amines, formed by loss of both acyl functions. This type of cyclisation was not



	R	Time (h)	Yield
a)	H	3	52%
b)	Me	3.5	54%
c)	n-Pr	24	59%

Scheme 5

successful when applied to β-aryl allylic acetates derived from alcohols **7d** or **7e**, or to the *bis*-acetate obtained from the α,β-dimethyl derivative **7c**. In these cases, gross mixtures of products were obtained, despite many modifications to the catalyst, solvent and temperature.

In summary, we have defined a straightforward route to a new 1,2,3-triazolo[1,2]benzodiazepine heterocyclic ring system based on an intramolecular Michael addition. The presence of the 7-ketone function suggests that many other derivatives of this system could be accessed from these initial products. The opportunity for the incorporation of an at least reasonably diverse range of substituents suggests that this

chemistry could make a contribution to the ever-present requirement for new heterocyclic systems in the continuing search for novel pharmaceuticals and related compounds.

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5. *Cf* Somei, M.; Natsume, M. *Tetrahedron Lett.*, **1974**, 461. Benzotriazole **4** (1 equiv.) and powdered potassium hydroxide (5 equiv.) were vigorously stirred together in dry dimethylformamide (DMF; 3 ml g^{-1} of benzotriazole) then hydroxylamine-*O*-sulfonic acid (2 equiv.) was added portionwise such that the temperature remained below 50°C. After the addition, stirring was continued until the reaction mixture had cooled to ambient temperature then the solvent was removed by rotary evaporation. The residue was dissolved in a minimum of 2M aqueous hydrochloric acid and the solution refrigerated overnight to give 1-aminobenzotriazole hydrochloride, m.p. 131-4°C as colourless crystals of ≥95% purity. The free base **5** was obtained by basification using 2M NaOH followed by extraction into ether. The extracts were dried ($MgSO_4$) and evaporated to give amine **5** (67%), m.p. 84°C [Lit.[4] m.p. 84°C].
6. Satisfactory spectroscopic and analytical data have been obtained for all compounds reported herein.
7. Attenburrow, J; Cameron, A.F.B; Chapman, J.H; Evans, R.M; Hems, B.A.; Jansen, A.B.A.; Walker, T. *J. Chem. Soc.*, **1952**, 1094.
8. We are grateful to Professor M.B. Hursthouse and Mr D.E. Hibbs (Cardiff University) for these data, full details of which will be published elsewhere.
9. For example, benzodiazepine **9b** showed δ_H (400 MHz, $CDCl_3$, 300°K) 1.04-1.18 (3H, br d, 5-Me), 1.30-1.42 (9H, br s, Bu^t), 3.12 (1H, br d, *J* ~17, 6-H_A), 3.30 (1H, br d, *J* ~17, 6-H_B), 4.80-4.97 (1H, br res., 5-H), 7.49 (1H, t, *J* 7.6, 9-H), 8.24 (1H, d, *J* 7.6) and 8.29 (1H, d, *J* 7.6); δ_H ($CDCl_3$, 340°K) 1.21 (3H, d, *J* 7.2, 5-Me), 1.37-1.45 (9H, br s, Bu^t), 3.14 (1H, dd, *J* 18.3 and 4.4, 6-H_A), 3.32 (1H, dd, *J* 18.3 and 3.8, 6-H_B), 4.84 (1H, m, 5-H), 7.51 (1H, app. t, *J ca.* 7.9, 9-H), 8.29 (1H, d, *J* 7.5) and 8.32 (1H, d, *J* 8.2).
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11. W have recently found that even the use of ethyl acetate as a solvent for column chromatography of *N*-Boc-1-aminobenzotriazole derivatives is unwise, due to variable amounts of *N*-acetylation.

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