Notes

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Neurotropic and Psychotropic Agents. V.[1] An Improved Synthesis of 7-Chloro-5-(2-chlorophenyl)-2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine and Related Compounds[2]

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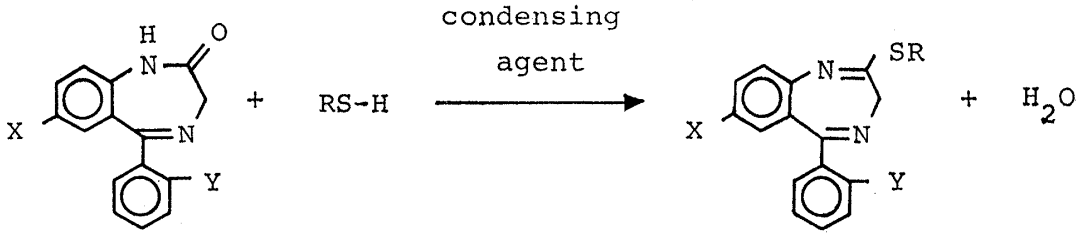
An improved method for the synthesis of 7-chloro-5-(2-chlorophenyl)-2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine (IIa) and related compounds is described. IIa was obtained in 75.1% yield by the reaction of the 1,4-benzodiazepin-2-one (Ia) with 2-dimethylaminoethanethiol in the presence of titanium tetrachloride; a small amount of 7-chloro-5-(2-chlorophenyl)-2-dimethylamino-3*H*-1,4-benzodiazepine (III) was obtained as a by-product. A mechanistic interpretation of the formation of III is presented.

Keywords——2-substituted thio-3*H*-1,4-benzodiazepine; Lewis acids; titanium tetrachloride; dialkylaminoalkanethiol; dimethylamine

In the previous paper,[1] we described the synthesis of 7-chloro-5-(2-chlorophenyl)-2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine (IIa) and related compounds from 1,3-dihydro-2*H*-1,4-benzodiazepine-2-ones (I) *via* 1,4-benzodiazepine-2-thiones. In order to develop a simpler and more efficient synthetic route to 2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine derivatives (II) we concentrated our attention on a one-step synthesis of II from the lactams (I) as illustrated in Chart 1.



I
a : X=Y=Cl
b : X=Cl Y=H
c : X=NO_2 Y=Cl
d : X=Cl Y=F

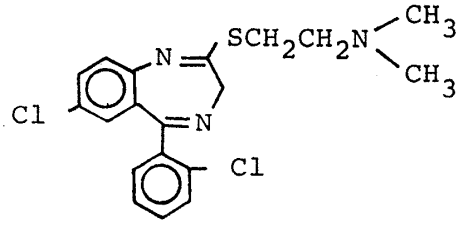
II

Chart 1

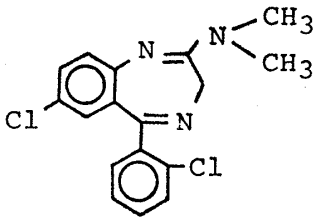
Previously, we reported the use of titanium tetrachloride ($TiCl_4$) for the preparation of enamines[3a] and of amides.[3b] Fryer *et al.* reported a synthesis of amidines from the lactam Ib and amines in the presence of $TiCl_4$.[3c] Thus, $TiCl_4$ has been shown to act as a useful condensing agent. We therefore attempted to synthesize II by the reaction of I with alkylaminoalkanethiols in the presence of $TiCl_4$.

When the lactam (Ia) was allowed to react with 2-dimethyl aminoethanethiol (DMET) in the presence of $TiCl_4$ in refluxing toluene, the desired compound (IIa) was obtained in 64.3% yield together with 2-dimethylamino-3*H*-1,4-benzodiazepine (III) as a by-product. The

structure of III was confirmed by direct comparisons with an authentic sample prepared according to the method described in the literature.[4] Other Lewis acids were also examined for the preparation of IIa. The reaction with tetrachlorosilane ($SiCl_4$) instead of $TiCl_4$ gave



IIa



III

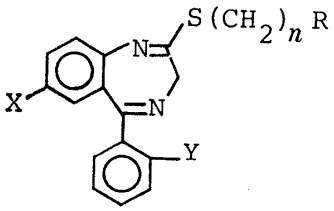
Chart 2

Table I. Reaction of Ia with 2-Dimethylaminoethanethiol (DMET) in the Presence of Lewis Acids ($TiCl_4$ and $SiCl_4$)

Method	Time (h)	Mol ratio of Ia : DMET	Condensing agent	Yield(%)[a] IIa	Yield(%)[a] III
A	1.5	1 : 4	$TiCl_4$ 1.5	75.2	2.3
A	2	1 : 8	$SiCl_4$ 2	62.0	n.d.
B	2	1 : 8	$TiCl_4$ 2	64.3	3.6
C	3	1 : 8	$TiCl_4$ 2	51.6	14.8

n.d.: Not detected.
a) Yields were determined by gas chromatography.

Table II. Preparation of 2-Substituted Thio-3*H*-1,4-benzodiazepines (II)



	X	Y	*n*	R	Solvent[a]	Reaction Temp (°C)	Reaction h	(I)	Mol ratio of : $R(CH_2)_nSH$:	$TiCl_4$	Yield (%)
IIa	Cl	Cl	2	$N(CH_3)_2$	T	R[b]	2.0	1	: 8 :	2	61.7
	Cl	Cl	2	$N(CH_3)_2$	T	R	1.5	1	: 4 :	1.5	75.1
IIb	Cl	Cl	3	$N(CH_3)_2$	T	R	3.5	1	: 8 :	2	87.2
IIc	Cl	Cl	2	N⟨ ⟩	T	R	1.5	1	: 8 :	2	62.5
IId	Cl	Cl	6	$N(CH_3)_2$	T	R	1.5	1	: 8 :	2	77.7
IIe	Cl	Cl	2	H	T	90	2.5	1	: 8[c] :	2	68.0
IIf	Cl	Cl	3	H	T	R	0.5	1	: 8[c] :	2	64.8
IIg	Cl	Cl	4	H	T	R	0.75	1	: 8[c] :	2	67.6
IIh	Cl	H	2	$N(CH_3)_2$	T	R	1.5	1	: 8 :	2	63.0
IIi	NO_2	Cl	2	$N(CH_3)_2$	Ch	R	7.0	1	: 12 :	2	34.6
IIj	Cl	F	2	$N(CH_3)_2$	T	R	2.0	1	: 8 :	2	64.0

a) T: toluene. Ch: chloroform.
b) R: refluxing solvent.
c) 8 mol of triethylamine was added.

IIa in 62.0% yield without formation of the by-product (III). Other Lewis acids such as aluminum chloride, boron trifluoride, zinc chloride, zirconium chloride, phosphorus trichloride, and stannic chloride were not effective.

Yields of IIa were found to vary depending upon the order of addition of starting material (Ia) and reagents ($TiCl_4$ and DMET). The products in the reaction mixture were determined by gas chromatography under the conditions described in "Experimental." The best result was obtained by addition of a toluene solution of DMET to a mixture of the lactam (Ia) and $TiCl_4$ in toluene (Method A). In this case, compound IIa was obtained in 75.2% yield and the formation of III was minimized. Addition of $TiCl_4$ in toluene to a mixture of Ia and DMET in toluene gave IIa in 64.3% yield (Method B). Addition of Ia in toluene to a mixture of DMET and $TiCl_4$ in toluene gave IIa in 51.6% yield (Method C). In the last case, the by-product (III) was obtained in 14.8% yield. The results are summarized in Table I.

A number of 1,4-benzodiazepines (II) were prepared by method A (procedure (i)) described in "Experimental," and the results are summarized in Table II.

In the formation of the by-product (III), compound IIa cannot be an intermediate, since it was recovered unchanged from the reaction of IIa with $TiCl_4$ in refluxing toluene for 19 h. Dimethylamine could be produced from DMET by the action of $TiCl_4$ and react with the lactam (Ia) in the presence of $TiCl_4$ to give III.[3c] In fact, when DMET was allowed to react with $TiCl_4$ in a 4: 1 mol ratio in refluxing toluene, dimethylamine was produced in a maximal yield of 12.6% as detected by gas chromatography of the corresponding *p*-benzenesulfonamide.

Experimental[5]

Solvents used were dried over molecular sieves 3A before use.

Dialkylaminoalkanethiols were prepared by the methods described in the literature:[6] 2-Dimethylaminoethanethiol, 61—66°C/65 mmHg (lit.[6a] 142—146°C/750 mmHg); 3-dimethylaminopropanethiol, 75—80°C/50 mmHg (lit.[6b] 40—41°C/12 mmHg); 2-piperidinoethanethiol, 115—120°C/40 mmHg (lit.[6a] 85°C/11 mmHg); 6-dimethylaminohexanethiol, 110—113°C/21 mmHg. 1,3-Dihydro-2*H*-1,4-benzodiazepin-2-ones (I) were prepared according to the methods described in the literature.[7]

7-Chloro-5-(2-chlorophenyl)-2-(2-dimethylaminoethylthio)-3*H*-1,4-benzodiazepine (IIa)[1] and 7-Chloro-5-(2-chlorophenyl)-2-dimethylamino-3*H*-1,4-benzodiazepine (III)——Procedure (i): A solution of Ia (1.5 g) and $TiCl_4$ (1.4 g) in dry toluene (15 ml) was refluxed for 10 min and then cooled to 40°C. A solution of DMET (2.1 g) in dry toluene (5 ml) was added to the resulting solution. After being stirred at 40°C for 15 min then for an additional 1.5 h under reflux, the mixture was cooled to room temperature. The toluene layer and solids were separated and the solids were washed with benzene. The organic layer was washed with 10% NaOH and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel with a (20: 1) mixture of $CHCl_3$ and MeOH to give IIa (1.45 g, 75.1%). It was converted into the corresponding maleate, mp 140—142°C (lit.[1] 140—142°C) (from AcOEt). In this case, III was not isolated.

Procedure (ii): A solution of $TiCl_4$ (1.9 g) in dry toluene (1 ml) was added to a solution of DMET (4.2 g) in dry toluene (15 ml) over 2 min at 20°C. After 10 min of stirring, Ia (1.5 g) was added to the resulting solution and the mixture was heated under reflux for 3 h. The resulting residue obtained on work-up as above was subjected to column chromatography on silica gel with a (20: 1) mixture of $CHCl_3$ and MeOH. The first eluate gave III (0.15 g, 9.2%), mp 159—162°C (from aq. EtOH). The following eluate gave IIa (0.87 g, 45.1%).

III was prepared according to the method described in the literature.[4] Yield: 32.9%. mp 159.5—162.5°C (from aq. EtOH). *Anal.* Calcd for $C_{17}H_{15}Cl_2N_3$: C, 61.46; H, 4.55; N, 12.65. Found: C, 61.34; H, 4.52; N, 12.54. IR ν_{max}^{Nujol} cm^{-1}: 1602, 1589, 1572. ^{1}H-NMR ($CDCl_3$) δ: 3.18 (6H, s, $N(CH_3)_2$), 4.13 (2H, bs, C_3–CH_2–), 6.97—7.43 (7H, m, Ar–H).

Other compounds[1] (II) prepared according to procedure (i) are summarized in Table II.

Determination of IIa and III in the Reaction Mixture by Gas Chromatography——The gas chromatograph was equipped with a flame ionization detector (FID). The column was OV-210 on high performance Chromosorb W, 80—100 mesh (1.0 m × 2.0 mm i.d.). Conditions used were: oven 200°C, injection part 246°C, hydrogen 0.8 kg/cm^2, air 2.0 kg/cm^2, nitrogen carrier gas 1.0 kg/cm^2, and chart speed 10 mm/min. t_R: IIa, 8 min; III, 4 min. The contents were measured by using calibration curves. The procedure is as follows. $TiCl_4$ (1.9 g) in dry toluene (1 ml) was added to a solution of Ia (1.5 g) and DMET (4.2 g) in dry toluene (40 ml) over 2 min at room temperature with stirring. After being stirred for 2 h under reflux and

then cooled to room temperature, the mixture was filtered and the solids on the filter were washed with benzene. The combined filtrate and washings were washed with 10% NaOH and H_2O, dried and concentrated *in vacuo* to give an oil, which was dissolved in AcOEt and injected into the gas chromatograph.

Determination of Dimethylamine in the Reaction Solution——The reaction mixture of DMET and $TiCl_4$ was treated with *p*-toluenesulfonyl chloride. The mixture was stirred for 30 min, adjusted to pH 8—9 with aqueous K_2CO_3 and filtered. The solids on the filter were washed with acetone. The combined filtrate and washings were concentrated *in vacuo*, and the residue was diluted with H_2O and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$, 5% HCl, and H_2O, then dried, and injected into the gas chromatograph.

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References and Notes

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5) All melting points were determined on a capillary melting point apparatus (Thomas Hoover) and are uncorrected. Infrared spectra were taken with a Hitachi 215 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with Varian EM-360 and JEOL MH-60 spectrometers using tetramethylsilane as an internal standard. The following abbreviations are used; s=singlet, bs=broad singlet, m=multiplet. Gas chromatography was carried out on a JEOL JGC-20K gas chromatograph.
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