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STEREOCHEMISTRY OF 2,4,6-TRIALKYL-1,3,5-TRIAZABICYCLO[3.1.0]HEXANES

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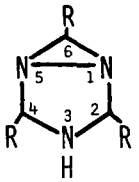
Addition of alkanals to chloramine in methanolic ammonia (-30°, 1 hr; 25°, 1 hr.) leads to 2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes (Schmitz reaction).[1] An alternate synthetic route to these materials and new examples of this reaction have been found (Table). The stereochemistry of the products and mechanism of their formation have been examined.

Products obtained by the Schmitz reaction were found to possess trans stereochemistry of the C-2,C-4 substituents. Separate signals were observed in the nmr spectrum for the C-2 and C-4 ring protons in those compounds where these signals could be resolved (Table; compound, R): 1a, CH_3; 2a, C_2H_5; 4a, i-C_3H_7; 7a, t-C_4H_9; 9a, $(C_2H_5)_2CH$; 10a, C_6H_5. Signal line broadening was observed for one of these signals. The broadening disappeared on addition of D_2O indicating coupling of one of the ring protons to NH. The remainder of the nmr spectrum for each compound is in agreement with structure assignments. For example, in 1a three distinct methyl doublets appear: δ 1.30, 1.32 (d, J = 6.5 Hz, 6H, C-2,C-4 CH_3); 1.37 (d, J = 5 Hz, 3H, C-6 CH_3); 2.25 (q, J = 5 Hz, 1H, C-6 CH).

Epimeric 2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes 1b, 2b, 3b and 4b having cis stereochemistry of the 2,4-dialkyl substituents have been prepared by t-butyl hypochlorite oxidation of 2,4,6-trialkyl-1,3,5-hexahydrotriazines 12a-d. These triazine precursors were assigned all equatorial stereochemistry in agreement with their nmr spectra.[2] Oxidations employed one mole-equivalent each of t-butyl hypochlorite and sodium carbonate in methanol at -40° (1 hr), followed by warming to ambient temperature (1-3 hr). This procedure was effective only for

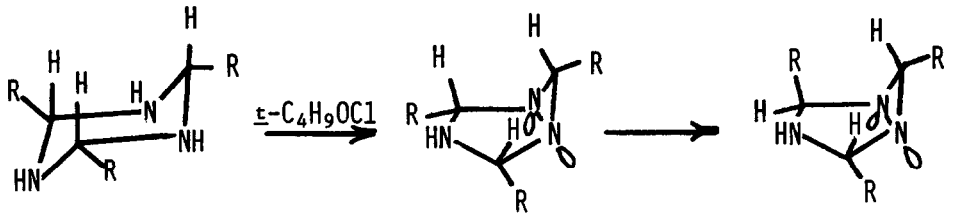
TABLE

2,4,6-Trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes



Cpd.	R	Prep. Method[a]	M.p. °C[b]	Molecular Formula[c]	C-2,C-4 Stereo.	Nmr signals; CH @ C-2,C-4 δ ppm[d]
1a	CH_3	A	111-113[e]	$C_6H_{13}N_3$	trans	4.42, 4.57 (q, J = 6.5 Hz)
1b	CH_3	B	106-108	$C_6H_{13}N_3$	cis	4.48 (q, J = 6.5 Hz)
2a	C_2H_5	A	98-100[f]	$C_9H_{19}N_3$	trans	4.05, 4.08 (t, J = 6 Hz)
2b	C_2H_5	B	91-93	$C_9H_{19}N_3$	cis	4.05 (t, J = 6 Hz)
3a	n-C_3H_7	A	82-84[g]	$C_{12}H_{25}N_3$	trans	3.95-4.25 m
3b	n-C_3H_7	B	66-69	$C_{12}H_{25}N_3$	cis	3.95-4.25 m
4a	i-C_3H_7	A	140-143	$C_{12}H_{25}N_3$	trans	3.70[h], 3.78 (d, J = 7.5 Hz)
4b	i-C_3H_7	B	i	$C_{12}H_{25}N_3$	cis	3.60 (d, J = 8 Hz)[j]
5a	n-C_4H_9	A,B	68-69	$C_{15}H_{31}N_3$	trans	3.9-4.2 m
6a	i-C_4H_9	A,B	134-139	$C_{15}H_{31}N_3$	trans	4.3 (apparent t, J ≃ 7 Hz)
7a	t-C_4H_9	A	93-95	$C_{15}H_{31}N_3$	trans	3.82 s; 4.18 s[h]
8a	n-C_5H_{11}	A,B	51-55	$C_{18}H_{37}N_3$	trans	3.9-4.25 m
9a	$(C_2H_5)_2CH$	A	145-147	$C_{18}H_{37}N_3$	trans	3.90 (d, J = 9 Hz); 3.98 (d[h], J = 8 Hz)[j]
10a	C_6H_5	A	162-164[k]	$C_{21}H_{19}N_3$	trans	5.25 s[h]; 5.62 s
11a	n-C_6H_{13}	A,B	65-67	$C_{21}H_{43}N_3$	trans	4.0-4.3 m

(a) Method A: from alkanal and chloramine in methanolic ammonia (30-60% yields of recrystallized product). Method B: from 2,4,6-trialkyl-1,3,5-hexahydrotriazines by t-butyl hypochlorite oxidation (6-20% yields in 2-4 hr @ 25°; 20-40% yields in 24-48 hr with epimerization of cis products).
(b) Capillary melting point of analytically pure samples crystallized from hexane, heptane or ether.
(c) Elemental analyses and molecular weight data agree with the theoretical values.
(d) Measurement in $CDCl_3$ at ca. 30°.
(e) lit.[1] mp 114-115°.
(f) lit.[1] mp 104-104.5°.
(g) lit.[1] mp 84-86°.
(h) Broadened signal.
(i) ca. 1:1 mixture of cis and trans forms by nmr assay, mp 126-128°.
(j) D_2O added to facilitate resolution.
(k) lit.[1] mp 160-162°.



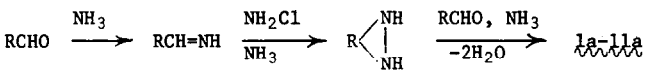
12a-d 1b-4b 1a-4a

reactants having relatively small R groups (CH_3, C_2H_5, n-C_3H_7). Reactants having alkyl groups larger than C_3H_7 produced triazabicyclo[3.1.0]hexanes 5a, 6a, 8a and 11a having C-2,C-4 trans stereochemistry only (Table). 2,4,6-Triisopropyl-1,3,5-hexahydrotriazine gave a mixture of cis and trans products, 4a,b.

The structure and stereochemistry of cis compounds 1b-4b is evident from their method of synthesis and examination of their nmr spectra (Table). The C-2,C-4 ring proton signals are equivalent. The remainder of the spectrum is in agreement with the cis structure. For example in 1b (R = CH_3): δ 2.12 (q, J = 5 Hz, 1H, C-6 CH); 1.39 (d, J = 7 Hz, 6H, CH_3 @ C-2,C-4); 1.29 (d, J = 5 Hz, 3H, CH_3 @ C-6).

Epimerization of cis isomers 1b-4b to trans 1a-4a occurs quantitatively in methanol at 25° within 48 hr. The epimerization is believed to occur so rapidly in products having larger alkyl groups (R = C_4H_9 and larger) that the cis isomers cannot be isolated under the reaction conditions. The R groups are assumed to be all exo in cis isomers 1b-4b. One of the R groups (C-2 or C-4) would be endo in trans isomers 1a-11a. The exocyclic hydrazino nitrogen p lobes facilitate the cis ⟶ trans epimerization.

The mechanism of formation of triazabicyclo[3.1.0]hexanes in the Schmitz reaction has been considered to involve a diaziridine intermediate (13).[1] An alternate route involving prior



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2,4,6-trialkyl-1,3,5-hexahydrotriazine formation (12), followed by chloramine oxidation to 1a-11a is possible, and has been observed by us (12b ⟶ 2b), but is not generally applicable

under Schmitz reaction conditions. Triazine (12) formation occurs in 10M methanolic ammonia, but very slowly at -30° and only with aldehydes which produce such triazines in 15 M ammonia.[2] Certain aldehydes which form no triazines (12, R = t-C_4H_9, $(C_2H_5)_2CH$, C_6H_5) form triazabicyclo-[3.1.0]hexanes (7a, 9a, 10a) readily under conditions of the Schmitz reaction. It is concluded that aldimine and diaziridine formation are usually more rapid than competitive 2,4,6-trialkyl-1,3,5-triazine formation, except possibly for an aldehyde such as acetaldehyde where these rates might compete. Epimerization of cis products 1b-4b to trans 12-4a occurs rapidly in 10 M methanolic ammonia so that no mechanistic conclusions can be drawn from product stereochemistry.

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