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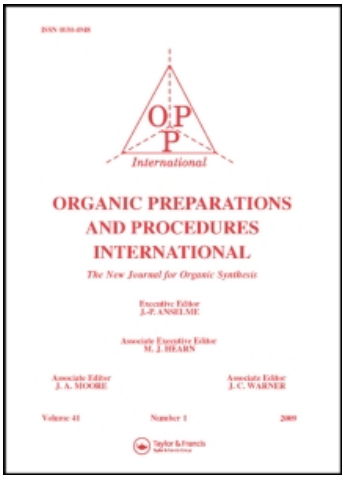

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A MODIFIED SYNTHESIS OF AMINOBICYCLO[n.1.0]ALKANES FROM ENAMINOSULFONIUM SALTS

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OPPI BRIEFS

A MODIFIED SYNTHESIS OF AMINOBICYCLO[n.1.0]ALKANES FROM ENAMINOSULFONIUM SALTS

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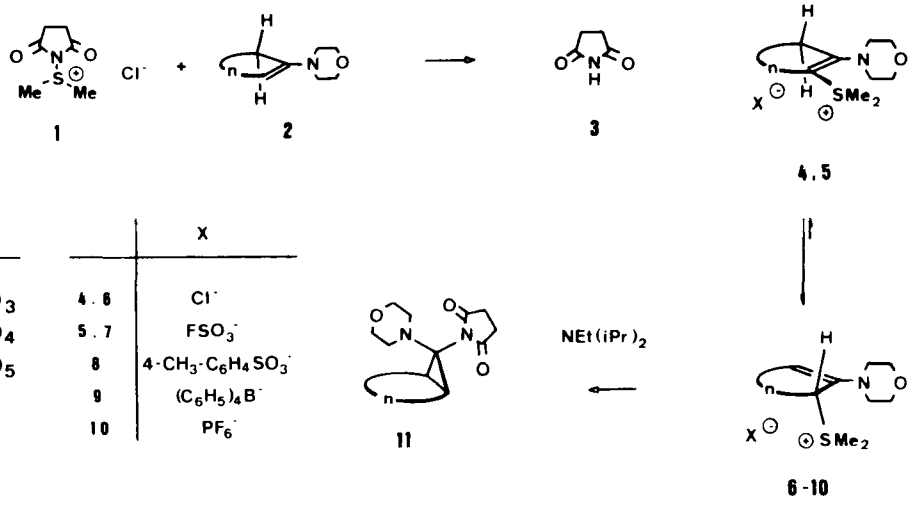
A great variety of aminobicyclo[n.1.0]alkane derivatives have been synthesized by the reaction of enaminosulfonium fluorosulfates (7) with nucleophiles.[1-5] The reaction of 7 with succinimide 3 in the presence of a tertiary amine led to bicyclic compounds 11, which can be used to introduce further substituents into the aminobicycloalkyl system.[5-10] Enamine 2 and



	n
a	$(CH_2)_3$
b	$(CH_2)_4$
c	$(CH_2)_5$

	X
4, 6	Cl^-
5, 7	FSO_3^-
8	$4\text{-}CH_3\text{-}C_6H_4SO_3^-$
9	$(C_6H_5)_4B^-$
10	PF_6^-

imidosulfonium chloride 1 were starting materials for a two-step preparation of enaminosulfonium fluorosulfates 7. Since enaminosulfonium chlorides 6, the primary products from 1 and 2 possessing a normal or medium large ring system, gave bicyclic derivatives 11 only in low yields, they were converted to sulfonium fluorosulfates 7 by addition of methyl

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fluorosulfate. However, the toxicity and the high cost of methyl fluorosulfate prompted us to devise a modification of the aminobicyclo[n.1.0]alkane synthesis by using enaminosulfonium salts of p-toluenesulfonate, tetraphenylborate or hexafluorophosphate counterions as starting materials.

The sulfonium tetraphenylborate 9b and the hexafluorophosphate 10b were easily obtained as crystalline precipitates from aqueous solutions of sodium tetraphenylborate or ammonium hexafluorophosphate and sulfonium chloride 6. Exchange of chloride by p-toluenesulfonate was best achieved by stirring a dichloromethane solution of 6 with an aqueous solution of excess sodium p-toluenesulfonate. Sulfonium salts 8b, 9b and 10b were isolated as pure substances and characterized by ^{1}H NMR spectroscopy and elemental analyses (Table 1). Attempts to bind chlorine by complexation with antimony pentachloride were not successful.

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TABLE 1. Yields, Physical Data and Elemental Analyses of Enaminosulfonium Salts

	Yield (%)	mp. (°C)	^{1}H NMR ($CDCl_3$, 200 MHz) $^+S(CH_3)$ (s)	>CH- (t)	>CH-S^+ (m)	Elemental Analyses (Found)		
8b	81	91°	3.1, 3.2	5.2	5.0	58.1 (57.8)	7.6 (7.4)	3.4 (3.3)
9b	62	144°	0.8, 1.3	5.3	3.0	79.1 (78.8)	7.8 (7.8)	2.5 (2.4)
10b	63	112°	2.86,2.89	5.4	4.35	39.7 (39.7)	7.7 (7.0)	3.6 (3.5)

Sulfonium salts (8b, 9b and 10b) succinimide and ethyldiisopropylamine upon heating in acetonitrile, afforded after the usual work-up, pure succinimido bicycles 11b in 52% (from 10b), 51% (from 9b) and 46% (from 8b) yields. Since exclusion of moisture was necessary for the formation of 11, the sulfonium salts had to be thoroughly dried after anion exchange.

Consequently, in this case anhydrous conditions are preferred for the anion exchange. Best results were obtained by stirring 5 in acetonitrile with a mixture of sodium p-toluenesulfonate and sodium sulfate; the filtered solution may be used directly for the preparation of 11. By this method bicyclic compounds 11 were obtained in 35% (11a), 58% (11b) and 39% (11c) yield; these yields are based on 2. In spite of slightly lower yields (in one case higher yields), enaminosulfonium p-toluenesulfonates proved to be more suitable for a convenient and facile preparation of aminobicyclo[n.1.0]alkane derivatives 11 than the corresponding enaminosulfonium fluorosulfates 7.

EXPERIMENTAL SECTION

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Dimethyl(2-morpholino-2-cycloheptenyl)sulfonium Toluenesulfonate (8b).- A solution of sulfonium chloride 6b (2.77 g, 10 mmol) in 50 ml of dichloromethane and a solution of p-toluenesulfonic acid (7 g, 30 mmol) in 50 ml of 10% NaOH were combined and stirred vigorously; after separation, drying and evaporation of the organic layer, the residue was triturated with ether to yield 8b.

Dimethyl(2-morpholino-2-cycloheptenyl)sulfonium Tetraphenylborate (9b).- Solutions of 3.42 g (10 mmol) of sodium tetraphenylborate and 2.77 g (10 mmol) of 6b each in 80 ml of water were combined. The precipitate was collected and washed twice with water (20 ml).

Dimethyl(2-morpholino-2-cycloheptenyl)sulfonium Hexafluorophosphate (10b) was obtained in a similar manner from 2.77 g (10 mmol) of 6b and 2.45 g (15 mmol) of ammonium hexafluorophosphate in water (120 ml).

N-(endo-7-Morpholinobicyclo[4.1.0]hepty1)succinimide (11b) from Enaminosulfonium Salts 8b, 9b and 10b.- A mixture of 5 mmol cycloheptenylsulfonium salt (8b: 2.07 g; 9b: 2.85 g; 10b: 1.87 g), 0.64 g (5 mmol) of ethyldiisopropylamine and 0.49 g (5 mmol) of succinimide was heated in 40

ml of acetonitrile (8b: 60°C, 1 day; 9b: 80°C, 3 days: 10b: 60°C, 3 days). Evaporation of the solvent and subsequent washing with 30 ml of 5% KOH and 20 ml of pentane followed by recrystallization from 10 ml of ethanol gave pure 11b: 0.66 g (46%, from 8b); 0.73 g (51% from 9b); 0.76 g (52% from 10b); mp. 190-192°, lit.[5] 184°. ^{1}H NMR ($CDCl_3$): δ 3.7 (H_A), 3.5 (H_B), 2.8 (H_X), 2.4 (H_Y) (ABXY-system: J_{AB} = 12.0 Hz, J_{XY} = 12.0 Hz, J_{BY} = 11.8 Hz), 2.6 (m, 4H, succinimide), 1.8-2.0 (m, 2H), 1.6-1.8 (m, 2H), 1.4-1.6 (m, 2H), 1.1-1.4 (m, 4H).

N-(endo-Morpholinobicyclo[n.1.0]alkyl)succinimides (11a-c) from Enamines 2a-c.- To a solution of 53.4 g (0.4 mol) of N-chlorosuccinimide in acetonitrile (700 ml) was added dropwise 29.3 ml (0.4 mol) of dimethylsulfide at -20°. After 30 min. of stirring at -20°, 0.4 mol of enamine (2a: 66.9 g; 2b: 72.5 g; 2c: 78.1 g) was added dropwise to the suspension, which became clear after the addition was complete. The temperature of the solution was allowed to become ambient and then a mixture of 100 g (0.46 mol) of sodium p-toluenesulfonate (containing 10% of water) and 50 g of sodium sulfate was added [in the case of 1 and 2b,c, the reaction mixture has to be stored at room temperature for 15 hrs prior to the addition of the sulfonate-sulfate salts]. The suspension was vigorously stirred for 2 hrs and then centrifuged; the solid was collected, washed with 250 ml of acetonitrile and separated again by centrifugation. To the combined acetonitrile solution, excess succinimide (39.6 g, 0.4 mol) and 58.2 g (0.45 mol) of ethyldiisopropylamine were added. Heating at reflux (2a: 6 hrs; 2b: 23 hrs; 2c: 25 hrs) followed by evaporation of the solvent and washing with 10% KOH solution (300 ml) and pentane (200 ml) afforded 11a-c.

11a: 37.5 g (35%), mp. 190°, lit.[5] 191°.

11b: 64.1 g (58%), mp. 189°, lit.[5] 184°.

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11c: 45.8 g (39%), mp. 193°, lit.[5] 193°.

^{1}H NMR spectra ($CDCl_3$): 11a: δ 3.7 (H_A), 3.5 (H_B), 2.8 (H_X), 2.4 (H_Y) (ABXY-system J_{AB} = 10.4 Hz, J_{XY} = 12.0 Hz. J_{BY} = 11.5 Hz), 2.7 (m, 4H, succinimide), 1.65-2.1 (m, 8H). 11c: δ 3.7 (H_A), 3.5 (H_B), 2.65 (H_X), 2.4 (H_Y), (ABXY-system, J_{AB} = 10.3 Hz, J_{XY} = 10.8, J_{BY} = 11.2 Hz), 2.6 (m, 4H, succinimide), 2.0-2.4 (m, 2H), 1.7-1.95 (m, 2H), 1.1-1.55 (m, 8H).

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