A NOVEL ACCESS TO 3-BENZAZEPINES AND TO 3-BENZOXEPINES VIA $S_{RN}1$ REACTIONS

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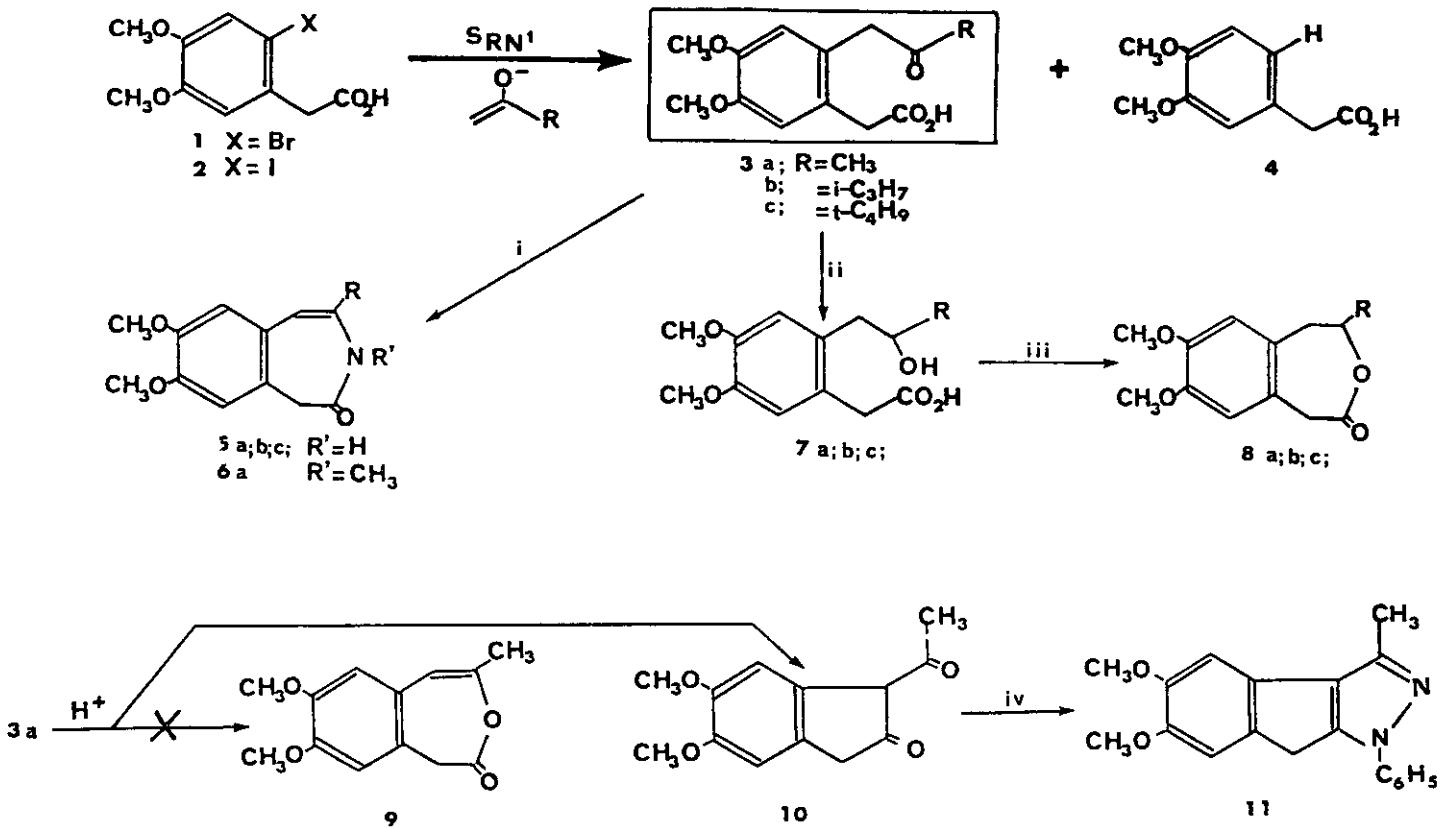
Abstract - A common intermediate formed by an $S_{RN}1$ reaction between halohomoveratic acid and various ketone enolates leads to either benzazepines (2a,b,c) or to benzoxepines (8a,b,c) in yields ranging from 50 to 70%.

The 2- and 3-benzazepines constitute a class of heterocyclic compounds of great interest, primarily because of their pharmacological properties[1] related to those of benzodiazepines. Therefore the search for new synthetic methods continues to be an active challenge.[2,3] Benzoxepines, on the other hand although less intensively studied[4] are also interesting compounds. We report that the $S_{RN}1$ reaction which offers a wide scope for the synthesis of benzene fused 5 or 6 membered ring heterocycles,[5] also provides an easy access to both classes of the title heterocycles from a common intermediate.

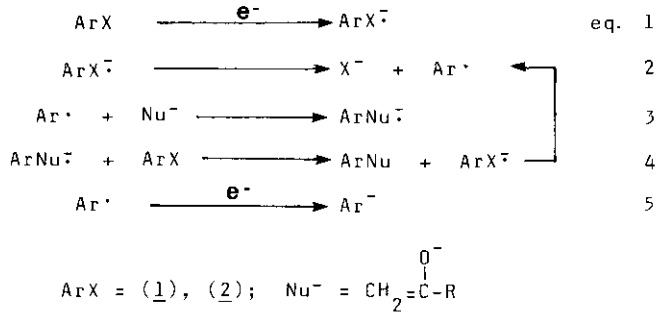
A photo-stimulated model reaction carried out on (1) (easily obtained from (4) by bromination) and the acetone derived enolate (R = CH_3) as nucleophile (exp. 1), led to (3a) (60%) together with (4) (40%). In the dark (exp. 2), under otherwise identical conditions no reaction occurred, which is consistent



i, $NH_4CO_2CH_3$, ; ii, $NaBH_4$; iii, DiCyclohexylCarbodiimide/4-dimethylaminopyridine

iv, $PhNH\text{-}NH_2$

with the $S_{RN}1$ mechanism leading to both the substitution product (3a) (eq. 1-4) and the reduction product (4) (eq. 5).



ArX = (1), (2); $Nu^- = CH_2=\overset{O^-}{\overset{|}{C}}-R$

For our synthetic purpose, the side reduction reaction had two unwanted features i) low yield of the substitution reaction leading to (3a); ii) long reaction time, eq (5) being a termination step in the radical chain process described by eq (1-4). Iodide is a better leaving group than bromide for the $S_{RN}1$ reaction[6a] and (2), in spite of its less direct preparation (77%), happened to be the substrate of choice for the synthesis of (3a,b,c) (exp. 3). This reaction is easily scaled up (exp. 5) indicating that the $S_{RN}1$ reaction is of preparative interest as reported on simpler cases.[6b]

Table 1. The $S_{RN}1$ key step reaction of 1 or 2 with enolates.

Exp.	Substrate (mmol)		Nucleophile (mmol)		Reaction time (min)	Substitution Product 3 (%)		Reduction Product 4 (%)
1	(1)	1	$CH_2=\overset{O^-}{\overset{|}{C}}-CH_3$	4	180	3a	60	40
2	(1)	1	-id-	4	180[a]		0	0
3	(2)	1	-id-	4	25	3a	75-80	20-25
4	(2)	1	$CH_2=\overset{O^-}{\overset{|}{C}}-i-C_3H_7$	4	15	3b	85-90	10-15
5	(2)	10,5	-id-	29	30	3b	75	25
6	(2)	1	$CH_2=\overset{O^-}{\overset{|}{C}}-t-C_4H_9$	4	15	3c	85-90	10-15

[a] in the dark

The treatment of (3a,b,c) upon ammonium acetate by a procedure adapted from the one reported for the formation of 6-membered ring lactams[7] led respectively to (5a) (50%) which being poorly soluble was converted to (6a), (5b) (60%) and (5c) (56%). The benzoxepines (9) could in principle be formed under acidic conditions, but such was not the case and the acylindanone (10),[8] characterized by its phenylhydrazine derivative[9] (indeno-pyrazole) (11) was obtained, whereas the tetrahydro-3-benzoxepin-2-ones (8a,b,c) were obtained by lactonization of the intermediate alcohols (7a,b,c).

EXPERIMENTAL

The starting materials were prepared by halogenation of homoveratric acid according to literature procedures. (1) mp 116°C (lit.[10] mp 115°C); ^{1}H NMR δ: 3.75 (s, 2H), 3.83 (s, 6H), 6.79 (s, 1H), 7.01 (s, 1H). (2) mp 170-172°C (lit.[11] mp 164-165°C); ^{1}H NMR δ: 3.77 (s, 2H), 3.83 (s, 6H), 6.80 (s, 1H), 7.25 (s, 1H).

General procedure ($S_{RN}1$ reaction) for the preparation of compounds (3a,b,c). (1) or (2) (1 mmol) and freshly sublimed K-O-t-Bu (5 mmol) introduced in a Pyrex three necked flask fitted with a dry ice condenser and rubber caps are dissolved in liquid ammonia (60 ml) prepared by condensing ammonia gas at -33°C under argon. The corresponding ketone (4 mmol) is then added through the cap by a syringe. The reaction on (1) (exp. 1) was illuminated in a Rayonet apparatus (S.O. England C°) equipped with four R.U.L. 3000 tubes whereas the reactions on (2) (exp. 3-6) were illuminated with a medium pressure UV lamp (Hanau Q81). The exp. 5 was carried out similarly, on (2) (3.3 g, 10.5 mmol) treated with methyl isopropyl ketone (3 ml, 29 mmol) and K-O-t-Bu (4.80 g) in liquid ammonium (500 ml). The reaction was illuminated for 30 min by two 100 W (Hanau Q81) lamps. The reactions were monitored by analyzing (t.l.c.) aliquots and quenched with ammonium chloride after consumption of (1) or (2). The work up was as follows: evaporation of the solvent, addition of brine, neutral and acidic extraction by CH_2Cl_2. The crude $S_{RN}1$ product mixture of acids (3a,b,c) and (4); ratio 3/4 estimated by NMR] was used without further purification (difficult at the stage) for the synthesis of (5a,b,c) and (8a,b,c) whose yields were thus based upon (2).

General procedure for the syntheses of benzazepines. The crude product of the $S_{RN}1$ reaction (0.160 g), added with ammonium acetate (2 g), was slowly heated to 120°C in glacial acetic acid (4 ml), and refluxed during 3h (t.l.c. monitoring) according to lit.[7] After cooling and basification by slow addition of solid Na_2CO_3 (3.5 g), CH_2Cl_2 extraction yielded the expected 7-membered ring lactam. The aqueous solution was acidified by addition of a few drops of concentrated HCl and extracted with CH_2Cl_2. Evaporation of the solvent gave essentially (4).

General procedure for the synthesis of benzoxepines (8a,b,c).

1) Reduction of the keto-acids. The crude product of the $S_{RN}1$ reaction (0.100 g) dissolved in methanol (5 ml) was stirred at room temperature for 30 min with sodium borohydride (0.100 g). Addition of brine and acidic work up (CH_2Cl_2) yielded the crude hydroxy acids (7a,b,c) used without further purification.

2) Cyclization of the hydroxy acids. This reaction was carried out on the crude (7a,b,c) by an efficient method;[12a,b] final purification was achieved by silica gel column chromatography.

1-Acyl-5,6-dimethoxy-indan-2-one (10)

Heating the crude $S_{RN}1$ product (3a) in benzene with p-toluenesulfonic acid did not yield the expected 3-benzoxepine (9) but instead the unstable compound (10) (65%), M.S. m/e 234 (M^+); ^1H NMR δ: 2.35 (s, 3H, CO-C<u>H</u>$_3$), 3.45 (br s, 2H, arom). Crude (3b) pr (3c) under similar treatment led to no isolable product.

5,6-Dimethoxy-1,8-dihydro-indeno[2,1-c]pyrazole (11)

(11) was obtained according to a procedure reported for the treatment of the 1-acyl-indan-2-one with phenylhydrazine.[9] mp 146-148°C; M.S. m/e 306 (M^+); ^1H NMR δ: 2.52 (s, 3H, C-C<u>H</u>$_3$), 3.77 (br s, 2H, C<u>H</u>$_2$-C$\begin{matrix}C\\ \diagdown C\end{matrix}$), 3.77-2.92 (two s, 6H, 5,6-OC<u>H</u>$_3$), 7-7.85 (m, 7H, arom). Anal.Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 73.99; H, 5.99; N, 9.04.

Benzazepines 5a,b,c; 6a

	Yield [%]	Mp [°C][a]	Molecular Formula[b]	M.S. [m/e]	IR [cm^{-1}]	^1H N.M.R. $CDCl_3$ [ppm]
5a[c]	50	236		233 (M^+)		
6a		108-113	$C_{14}H_{17}NO_3$ 247	247 (M^+) 232 (M^+-15) 217 (232-15)	1630, 1620	2.18(s,3H);3.05(s,3H) 6.35(s,1H);6.69(s,1H) 3.40(s,2H);3.85(s,6H) 6.78(s,1H)
5b	60	202-203	$C_{15}H_{19}NO_3$ 261	261 (M^+)	3350,1630,1620	1.2(d,6H);2.5(m,1H) 3.35(s,1H);3.86(s,6H) 6.21(s,1H);6.73(s,1H) 6.8(s,1H);8.0(b.s.,1H).
5c	56	177-179	$C_{16}H_{20}NO_3$ 275	275 (M^+)	3350,1630,1620	1.25(s,9H);3.35(s,2H) 3.36(s,6H);6.37(s,1H) 6.77(s,2H);7.5(b.s.2H).
Benzoxepines 8a,b,c						
8a	70	150-153	$C_{13}H_{16}O_4$ 236	236 (M^+)	1730,1720	1.50(d,3H);3.10(d,2H) 3.45(b.d.,J = 15 Hz,1H) 3.80(s,6H);4.4(b.d., J = 15 Hz,1H);4.8-5.3 (m,1H);6.6(b.s,2H).
8b	65	130-132	$C_{15}H_{20}O_4$ 264	264 (M^+)	1730,1720	1.05(d,6H);1.7-2.2(m,1H) 3.2(d,2H);3.45(d,J = 15 Hz,1H);3.8(s,6H);4.2-4.8 (m,1H);6.6(b.s.,2H).
8c	63	168-170	$C_{16}H_{22}O_4$ 278	278 (M^+)	1730,1720	1.08(s,9H);3.1(d,2H); 3.45(d,J = 15 Hz,1H); 3.8(s,6H);4.2-4.8(m,1H); 6.6(b.s.,2H).

[a]Melting points were not corrected. [b]Satisfactory microanalysis obtained: C ± 0.20; H ± 0.15; N ± 0.20 except 5c (C + 0.35). [c]5a Being very poorly soluble for IR and NMR determination was alkylated by $BrCH_3$ under phase transfer conditions and gave 6a which was fully analyzed.

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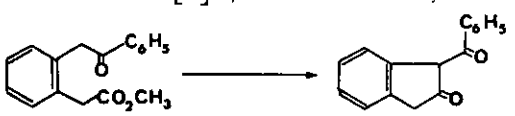

[I] [II]

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