Tetrahedron Vol. 29, pp. 2951 to 2953. Pergamon Press 1973. Printed in Great Britain

A NEW METHOD FOR ALKYLATING ISOQUINOLINIUM SALTS AT THE 4 POSITION

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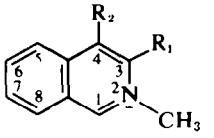
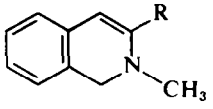
(*Received in the USA* 3 *December* 1972; *Received in the UK for publication* 30 *April* 1973)

Abstract—Alkylation and acylation of 2,3-dimethylisoquinolinium iodide at position 4- may be carried out in alkaline aqueous acetone. Presumably 1-acetonyl-2,3-dimethyl-1,2-dihydroisoquinoline is an intermediate. Lower yields were obtained in similar reactions with 2-methylisoquinolinium iodide.

The recently reported additions of vinyl ethers[1,2] or cyclopentadiene[3] to the 2,3-dimethylisoquinolinium cation **1** are the first examples of simple 1,4-cycloaddition reactions involving an isoquinolinium nucleus. Since analogy with the acridizinium system[4] suggests that substitution at position 4 might accelerate the cycloaddition, we have explored the



1: $R_1 = CH_3$, $R_2 = H$
2: $R_1 = CH_3$
3: $R_1 = R_2 = H$
4: $R_1 = H$



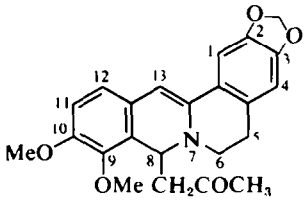
5: R = H
6: R = CH_3

methods available for the synthesis of 2,3,4-trisubstituted isoquinolinium salts **2**.

Since cyclization methods, such as the modifications of the Pomeranz-Fritsch synthesis by Bobbitt *et al.*[5] seemed too complex and inconvenient for our purposes, the transformation of commercially available isoquinoline derivatives was examined.

It was suggested by Battersby[6] that 1,2-dihydroisoquinolines **5** should possess enamine character and be susceptible to electrophilic attack at position 4. While Dyke *et al.* were able to demonstrate that acylation,[7] and to a much more limited extent alkylation,[8] of 2-alkyl-1,2-dihydroisoquinolines **5** could be accomplished, it remains to be demonstrated whether useful extension of these methods could be made to 2,3-dimethyl-1,2-dihydroisoquinoline **6**.

An alternate method for creating an enamine of the 1,2-dihydroisoquinoline type would be the addition of the anion derived from acetone to the 2,3-dimethylisoquinolinium cation **1**. It has been known for some time[9] that berberine salts and their congeners will react with acetone in the presence of alkali to afford berberine acetone **7**, and it has been shown that these adducts may be alkylated[10] at position 13. Despite the similarity of berberine to 2,3-dimethylisoquinolinium salts **1** there appears to be no record of the conversion of the latter to a 1-acetonyl-3-methyl-1,2-dihydroisoquinoline **8**.



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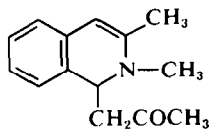


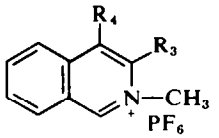
8 (not isolated)

This omission proved understandable, for although reaction of **1** with acetone in the presence of alkali gave an oil which in deuteriochloroform solution gave evidence of the presence of **8** when examined with NMR, the oil appears to be unstable and turns red on standing. Acidification of the oil resulted in an almost quantitative recovery of the 2,3-dimethylisoquinolinium salt **1**.

If two molar equivalents of sodium hydroxide is added to an acetone solution of **1** followed by the addition of benzyl bromide or an alkyl iodide, overnight stirring, followed by acidification, afforded the expected 4-alkyl-2,3-dimethylisoquinolinium salts **2** in better than 30% yield. Of the results recorded in Table 1 particularly notable are the alkylation with methyl iodide (41% yield) and with allyl bromide (34% yield) both representing types which failed with Dyke's alkylation procedure for 2-methyl-1,2-dihydroisoquinoline **5**. Side chains having functional groups were introduced through alkylation with ethyl iodoacetate and phenacyl iodide and by acylation (under modified conditions) with aroyl chlorides.

Although our major effort was directed to the synthesis of 4-substituted-2,3-dimethylisoquinolinium salts **1**, it was demonstrated that alkylation and aroylation of 2-methylisoquinolinium salts **3** at position 4 could be accomplished, although the yields were uniformly inferior to those obtained with the 2,3-dimethyl cation **1**.

Table 1. Preparation of 4-substituted isoquinolinium hexafluorophosphates



R_3	R_4	Procedure[a]	Yield, %	m.p., °C	Molecular formula	Analysis Found C	Found H	Found N	Requires C	Requires H	Requires N	Proton NMR, δ, ppm[b] C_1-H[c]	2-Me[d]	3-Me[e]	4-R
Me	Me	A	41	245·5–247	$C_{12}H_{14}NPF_6$	45·30	4·34	4·17	45·43	4·42	4·42	9·40	4·57	2·95	3·95 (s, 3H)
Me	$CH_2CH{=}CH_2$	A	34	167·5–169	$C_{14}H_{16}NPF_6$	48·77	4·47	3·97	48·98	4·66	4·08	9·37[f]	4·37	2·77	3·97–6·11[g]
Me	n-C_4H_9	C	28	188·9–190	$C_{15}H_{20}NPF_6$	50·14	5·57	3·90	50·22	5·68	3·74	9·90[h]	4·63	3·00	3·4 (m, 2H)[i]
Me	$CH_2C_6H_5$	A	54	227·5–229	$C_{18}H_{18}NPF_6$	55·05	4·53	3·34	54·96	4·58	3·56	9·88[h]	4·63	2·95	4·80 (s, 2H)
Me	$CH_2C_6H_4CH_3$ (*m*)	A	52	213·5–215·5	$C_{19}H_{20}NPF_6$	55·82	4·77	3·42	56·02	4·91	3·44	9·52	4·61	2·93	2·32 (s, 3H)[j]
Me	$CH_2COC_6H_5$	A	31	218·5–220	$C_{19}H_{18}NOPF_6$	53·98	4·03	3·36	54·16	4·28	3·33	9·57	4·60	2·90	5·33 (s, 2H)
Me	CH_2COOH	A[k]	41	208·5 (dec.)	$C_{13}H_{14}NO_2PF_6$	43·05	3·96	3·74	43·21	3·88	3·88	9·50	4·54	2·97	4·54 (s, 2H)
Me	COC_6H_5	B	51	238–239	$C_{18}H_{16}NOPF_6$	53·32	3·96	3·36	53·07	3·93	3·44	10·05[h]	4·62	2·78	—
Me	$COC_6H_4CH_3$ (*m*)	B	57	244·5–246	$C_{19}H_{18}NOPF_6$	54·43	4·11	3·37	54·16	4·28	3·33	9·70	4·63	2·80	2·47 (s, 3H)
Me	$COC_6H_4NO_2$ (*p*)	B	34	312 (dec.)	$C_{18}H_{15}N_2O_3PF_6$	47·47	3·52	6·32	47·78	3·31	6·19	9·80	4·64	2·80	—
Me	COC_6H_4OMe (*p*)	B	39	261–262·5	$C_{19}H_{18}NO_2PF_6$	52·17	4·03	3·12	52·17	4·12	3·20	9·70	4·63	2·83	4·03 (s, 3H)
H	Me	A	30	186·5–188	$C_{11}H_{12}NPF_6$	43·35	3·89	4·64	43·56	3·96	4·62	9·36	4·60	—	2·93 (s, 3H)
H	$CH_2C_6H_5$	A	40	185–186·5	$C_{17}H_{16}NPF_6$	53·64	3·97	3·59	53·83	4·22	3·69	9·40[l]	4·40	—	4·57 (s, 2H)
H	COC_6H_5	B	40	202·5–204·5	$C_{17}H_{14}NOPF_6$	52·07	3·62	3·47	51·91	3·56	3·56	9·64[l]	4·47	—	—

[a]Procedures described in Experimental. [b]All chemical shifts in the δ 6·0–9·0 region have been omitted. Except as noted all NMR spectra were measured in in CF_3COOH solution. [c]All C-1H resonances were one-proton singlets. [d]All 2-Me resonances were three-proton singlets. [e]All 3-Me resonances were three-proton singlets. [f]All resonances were measured in CD_3CN. [g]The resonances form a complex pattern but are easily assigned to an allyl group. [h]All resonances were measured in acetone -d_6. [i]At δ 1·0–1·6 multiplet of 7 protons. [j]At δ 4·76 a two-proton singlet. [k]The starting material was ethyl iodoacetate which underwent saponification at some stage in the reaction. [l]All resonances measured in CH_3CN.

It seems likely that the reported yields in all of these alkylations and acylations could be improved by modification of reaction conditions, and that electrophiles of other types might be used successfully.

EXPERIMENTAL

Reaction of 2,3-*dimethylisoquinolinium iodide* (1) *with acetone.* To a soln of 0·02 mole of 1 in 100 ml of a 1:1 (v.v) mixture of acetone and water, cooled in an ice bath, 10 ml of 10% sodium hydroxide soln was added. After the soln had been stirred for 20 min it was diluted with 150 ml of water and extracted with chloroform. After the chloroform extract had been washed with water and dried over anhydrous potassium carbonate the soln was conc under reduced pressure and the residual oil examined by NMR, δ 1·93 (s, 6H), 2·73 (d, 2H), 2·93 (s, 3H), 4·73 (t, 1H), 5·27 (s, 1H) and 6·90 (m, 4H).

When an acetone soln of the oil was acidified with hexafluorophosphoric acid it afforded an essentially quantitative yield of 2,3-dimethylisoquinolinium hexafluorophosphate.

Alkylation of 2,3-*dimethylisoquinolinium iodide. Procedure A*—To a soln containing 0·03 mole of 2,3-dimethylisoquinolinium 1 iodide in a mixture containing 80 ml of acetone and 80 ml of water, cooled in an ice bath, 0·075 moles of 10% sodium hydroxide was added. After stirring for 15–20 min 0·036 moles of the appropriate benzyl bromide or alkyl iodide (dissolved in acetone if a solid) was added. Stirring was continued and the mixture allowed to warm up to room temp overnight. The mixture was transferred to a polyethylene beaker and acidified with 12 g of hexafluorophosphoric acid. Most of the acetone was removed by blowing a stream of air over the surface of the liquid. The acidic reaction mixture was diluted with water and the solid collected and washed first with water and then with ethyl acetate. The air-dried crude product was crystallized from methanol–acetonitrile. *Procedure B*—The instructions for procedure A are followed except that only 0·033 mole of sodium hydroxide was added to generate the acetone adduct. After the 20 min stirring period, but before the benzoyl chloride was added 0·055 moles of sodium carbonate (as a 10% soln) was added, followed by addition of 0·08 mole of benzoyl chloride. The remainder of the procedure is identical with A. *Procedure C*—A mixture of 0·03 moles of 1 iodide, 0·06 moles of sodium carbonate soln and 0·036 moles of 1-iodobutane in 240 ml of 50% aqueous acetone was refluxed for 4 days in a stream bath. The solid was removed by filtration and washed with acetone. After acidification of the filtrate with hexafluorophosphoric acid, isolation was accomplished as in A.

Acknowledgement—The authors are indebted to the National Heart Institute (U.S.A.) for a grant.

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