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A NEW METHOD FOR THE SELECTIVE HALOGENATION OF THE METHYL GROUP OF METHYL KETONES

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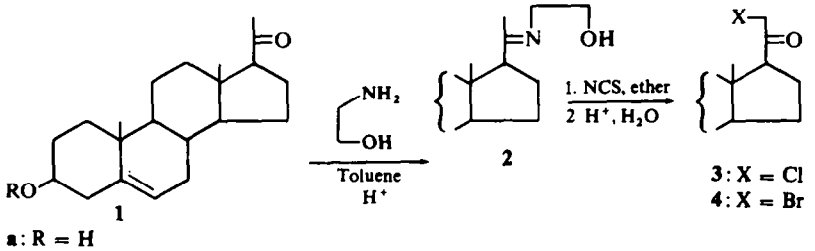
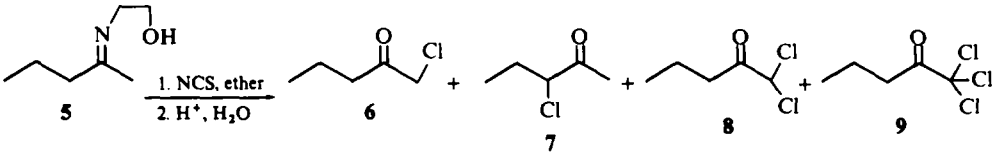
Abstract—Treatment of the ethanolamine-derived ketimine of two steroidal 20-ketones with either NCS or NBS in ether at 25° followed by mild acidic hydrolysis has led to the corresponding 21-haloketones in high yield. Application of this halogenation procedure to 2-pentanone demonstrated that this method may be general for the selective halogenation of the Me group of methylketones.

WE DESCRIBE herein a new method for the selective halogenation of the Me group of methyl ketones.[2] Treatment of pregnenolone **1a** with ethanolamine in toluene containing some Dowex-20 ion exchange resin (acid form) resulted in a 94% yield of the corresponding ketimine **2a**.[3] Similarly, the ketimine **2b** of pregnenolone acetate **1b** was prepared, although in lower yield (60%) due to partial removal of the acetate group by ethanolamine.[4] The NMR spectra of **2a** and **2b** required the "imine" structures shown since sharp 3-proton singlets were observed at δ 1·82 and 1·83, respectively, for the two substances, attributable to the C-21 Me groups.* The action of N-chlorosuccinimide (NCS) in ether at 25° on imines **2a** and **2b**, followed by direct treatment of the ether solutions with dilute hydrochloric acid as a second phase led in near quantitative yields to the respective 21-chloro derivatives **3a**[5] and **3b**.[5] Bromides **4a** and **4b**[6] could be prepared in 90% and 43% yields, respectively, utilizing N-bromosuccinimide (NBS) instead of NCS in an analogous manner. It will be noted that protection of the 5,6-double bond was not necessary.



In one preliminary test of the generality of this halogenation procedure N-2-pentylidene-ethanolamine (**5**)[7, 8] was treated as above with varying amounts of NCS. The relative yields of 1-chloro- (**6**),[9] 3-chloro- (**7**),[9] 1,1-dichloro- (**8**)[10] and 1,1,1-trichloropentan-2-one (**9**)[11] were determined by VPC and are shown in Table 1.

* The C_{21}-Me group of the corresponding oxazolidine structures would be expected to absorb in the δ 1·2–1·4 region of the spectra. The absence of this NMR absorption together with the presence of —C=N— absorption in the IR spectra at 1650 and 1640 cm^{-1} respectively, is conclusive evidence for the imine structures.



5 6 7 8 9

TABLE 1. PRODUCT DISTRIBUTION IN THE CHLORINATION OF IMINE 5 WITH NCS

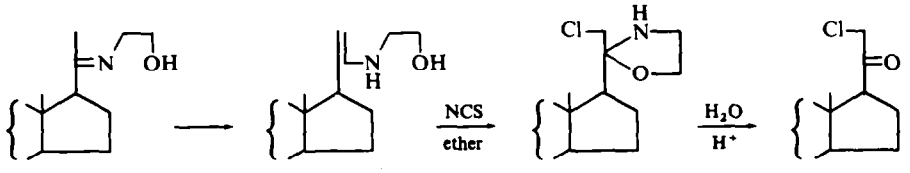
Molar ratio NCS/Imine	% Relative Yield 6	7	8	9	Other[a]
0·5	72	19	5	t[b]	t
1·0	39	11	50	t	t
2·0	11	4	61	16	8
3·0	t	t	15	70	15

[a] Sum of other unidentified materials appearing in the vapor phase chromatogram.

[b] t = trace.

The halogenation reaction probably proceeds *via* halogenation of the tautomeric enamine form **10** which could be present in solution at low concentration. Enamines are known to undergo ready reaction with bromine in dichloromethane, for example, leading after water treatment to the corresponding α-bromocarbonyl compound.[12]

In the NCS-imine **2b** reaction, evaporation of the ether prior to hydrolysis and trituration of the residue with hexane afforded, after three recrystallizations of the hexane-soluble portion from hexane, a crystalline intermediate which showed no absorption attributable to C=N in its IR spectrum. The NMR spectrum displayed two 2-proton triplets at δ 3·25 and 3·82 attributed to the ethanolamine moiety together with a 2-proton "AB" quartet (?) centered at δ 3·50 attributed to the C-21 protons. These data together with a chlorine analysis and a mass spectrum which showed an intense peak at *m/e* 399 (molecular ion less HCl) were consistent with expression **11** (tentative assignment). Treatment of an ether solution of intermediate **11** with dilute hydrochloric acid as above afforded a quantitative yield of chloride **3b**.



2b **10** **11** **3b**

EXPERIMENTAL

IR spectra were recorded with a Beckman IR-5A spectrophotometer. NMR spectra were determined on a Varian Associates Model A-60 high resolution spectrometer. Chemical shifts are recorded in ppm (δ) downfield from internal TMS, employing $CDCl_3$ as the solvent. Mass spectra were determined on a CEC-110 spectrometer (70 eV) equipped with a direct inlet attachment. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona. Solvents were routinely distilled prior to use. All chemicals were reagent grade. NBS and NCS were recrystallized from water and benzene, respectively, prior to use. M.ps were

determined in a stirred oil bath and are uncorrected. VPC analyses were performed on an 8' 5% SE-30 Chromsorb W column at 85°. Optical rotations were run in chloroform on a Perkin Elmer model 141 polarimeter.

N-(Pregn-5-en-3β-ol-20-ylidene)ethanolamine (**2a**). A mixture of 1·00 g (3·16 mM) of **1a**, 5 ml ethanolamine, 25 ml toluene and 100 mg Dowex 50-W resin (acid form) was refluxed in a flask fitted with a water separator. After 4 hr about 5 ml of a soln of ethanolamine and water had collected in the water separator. At this point an additional 2 ml ethanolamine was added to the flask. Heating was continued until a total of 7 ml of the ethanolamine-water soln had collected in the water separator. The contents of the flask was filtered while still hot, employing 5 ml boiling toluene as a rinse. Imine **2a** began to crystallize immediately from the filtrate. The mixture was allowed to stand at 6° overnight. The resulting crystals were collected by filtration, washed with cold hexane and dried, affording 1·02 g (90%) of **2a** as small colorless needles, m.p. 158–162°. A second crop, 40 mg (4%), m.p. 155–160°, was obtained from the mother liquor. Since Irmscher[3] reported m.p. 139° for **2a**, an analytical sample was prepared, m.p. 158–162°, by recrystallization from EtOAc: NMR δ 0·58 (s, 3, H-18), 0·99 (s, 3, H-19), 1·82 (s, 3, H-21), 3·2–3·8 (m, 1, H-3), 3·44 (t (J = 5 Hz), 2, ethanolamine moiety)), 3·72 (t(J = 5 Hz), 2, ethanolamine moiety)), 5·3–5·6 (m, 1, H-6); IR ($CHCl_3$), 3650 (w), 3417 (bd, w), 2960 (s), 1656 (m), 1438 (m), 1370 (m), 1238 (m), 1050 (s), 955 cm^{-1} (m); mass spectrum *m/e* 359 (molecular ion), 344 (loss of Me), 317, 316, 283, $[\alpha]_D^{25}$ − 16·0° (c, 10), (lit.[3] $[\alpha]_D^{25}$ − 15°). (Found: N, 3·85. Calcd. for $C_{23}H_{34}NO_2$: N, 3·90%).

An attempt to repeat the preparation by Irmscher's[3] procedure gave a solid, m.p. 139–147°, exhibiting an NMR spectrum consistent with a mixture of starting ketone and the desired imine.

N-(3β-Acetoxypregn-5-en-20-ylidene)ethanolamine (**2b**). Starting with 1·00 g of **1b** the above procedure gave, after the initial filtration and removal of the solvent, crude crystalline **2b**. Recrystallization from ether gave 685 mg (61%) of long colorless needles, m.p. 124–127°. A second recrystallization afforded the analytical specimen, m.p. 129–130°: NMR δ 0·59 (s, 3, H-18), 1·03 (s, 3, H-19), 1·83 (s, 3, H-21), 2·03 (s, 3, acetate), 3·32 (t (J = 5 Hz), 2, ethanolamine moiety), 3·80 (t (J = 5 Hz), 2, ethanolamine moiety), 4·4–4·8 (m, 1, H-3), 5·3–5·5 (m, 1, H-6); IR ($CHCl_3$) 3500 (w), 2975 (s), 1725 (s), 1650 (m), 1440 (m), 1378 (s), 1031 cm^{-1} (s); mass spectrum *m/e* 401 (molecular ion), 386 (loss of methyl) 369, 359. (Found: C, 74·45; H, 9·82; N, 3·47. Calcd. for $C_{25}H_{39}NO_3$: C, 74·77; H, 9·79; N, 3·49%).

Chloride intermediate **11**. To a soln of 200 mg (0·500 mM) imine **2b** and 30 ml ether under N_2 was added with stirring 67 mg (0·50 mM) of NCS. The clear soln was stirred for 2 hr after which time a small amount of precipitated succinimide was filtered off. Removal of the solvent gave a crystalline mass which was extracted with hot hexane. The extract was cooled, affording 125 mg of crude **11**. Three recrystallizations from hexane afforded 45 mg (21%) of white prisms which melted, turned bright yellow and resolidified when immersed in a m.p. bath at 120°. Below that temp the material slowly decomposed: NMR δ 0·82 (s, 3, H-18), 1·03 (s, 3, H-19), 2·02 (s, 3, acetate), 3·25 (t (J = 6 Hz), 2, ethanolamine moiety), 3·50 AB quartet, 2, H-21), 3·82 (t (J = 6 Hz), 2, ethanolamine moiety), 4·4–4·8 (m, 1, H-3), 5·3–5·5 (m, 1, H-6); IR ($CHCl_3$) 3400 (w), 2980 (s), 1725 (s), 1435 (m), 1375 (m), 1250 (s), 1040 cm^{-1} (s); mass spectrum *m/e* 399 (loss of HCl from molecular ion), 384, 339, 332, 298, 270. (Found: Cl, 8·14. Calcd. for $C_{25}H_{38}ClNO_3$: Cl, 8·13%).

21-Chloropregn-5-en-3β-ol-20-one (**3a**). To a soln of 180 mg (0·500 mM) imine **2a** in 75 ml ether was added 67 mg (0·500 mM) NCS. The clear soln was stirred at 25° for 2 hr and then 20 ml water containing 3 drops conc HCl was added and stirring was continued for another 2 hr. The layers were separated and the ether layer was washed with two 20-ml portions water and then dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded 170 mg (96%) of **4a** as small colorless needles, m.p. 153–157°. Recrystallization from MeOH gave 110 mg, m.p. 157–159° (lit. m.p. 162–164°): NMR δ 0·67 (s, 3, H-18), 1·02 (s, 3, H-19), 3·3–3·8 (m, 1, H-3), 4·11 (s, H-21), 5·20–5·50 (m, 1, H-6); IR ($CHCl_3$) 3626 (w), 2950 (s), 1721 (s), 1452 (m), 1388 (m), 1050 cm^{-1} (s).

21-Chloropregn-5-en-3β-ol-20-one (**3a**). To a soln of 180 mg (0·500 mM) imine **2a** in 75 ml ether was added quantitative yield of **4b** as small white plates, m.p. 142–148°. Recrystallization from EtOH afforded colorless needles, m.p. 152·5–154° (red melt) (lit. m.p. 153°, 157–158° after sublimation[4]): NMR δ 0·67 (s, 3, H-18), 1·02 (s, 3, H-19), 2·00 (s, 3, acetate), 4·08 (s, 2, H-21), 4·2–4·8 (m, 1, H-3), 5·2–5·5 (m, 1, H-6); IR ($CHCl_3$) 2978 (s), 1721 (s), 1441 (m), 1373 (m), 1252 (s), 1212 (s), 1032 cm^{-1} (s).

21-Bromo-3β-acetoxypregn-5-en-20-one (**4b**) Utilizing NBS and the above procedure 172 mg imine **2b** gave 178 mg crude **5b**. Recrystallization from MeOH gave 80 mg (43%) of **5b** as white needles, m.p. 145–147° (lit. m.p. 143–144·5°[5]): NMR δ 0·66 (s, 3, H-18), 1·02 (s, 3, H-19), 2·02 (s, 3, acetate), 3·90 (s, 1, H-21), 4·10 (s, 1, H-21), 4·3–4·8 (m, 1, H-3), 5·3–5·5 (m, 1, H-6); IR ($CHCl_3$) 2970 (s), 1728 (s), 1439 (m), 1380 (m), 1259 (s), 1037 cm^{-1} (s).

21-Bromo-3β-hydroxypregn-5-en-20-one (**4a**). Utilizing the above procedure with the exception of a longer (overnight) period to complete the hydrolysis step, **2a**, 180 mg (0·50 mM) gave upon treatment with 69 mg (0·50 mM) NBS, 196 mg of the 21-bromide m.p. 130–137°. Recrystallization from ether-pentane gave 178 mg (0·45 mM, 90%) of long colorless needles, m.p. 139–140°: NMR δ 0·68 (s, 3, H-18), 1·02 (s, 3, H-19), 3·3–3·8 (m, 1, H-3), 3·99 (s, 2, H-21), 5·3–5·6 (m, 1, H-6); IR ($CHCl_3$) 3600 (w), 1715 (s) cm^{-1}. Recrystallization from MeOH gave the analytical sample, m.p. 141–141·5°. (Found: C, 63·37; H, 8·07. Calcd. for $C_{21}H_{31}O_2Br$: C, 63·79; H, 7·90%).

Chlorination of 2-pentanone (Table 1). To stirred solns of 1·29 g (10·0 mM) N-2-(pentylidene)-ethanolamine,[7] n_D^{24} 1·4418, in 50 ml dry ether was added solid NCS in the molar ratios shown in Table 1. After 2 hr the precipitated succinimide was removed and the solns were hydrolyzed with 30 ml water containing 3 drops conc HCl for 2 hr. In the case where the ratio NCS/imine was 3·0 the reaction was allowed to proceed overnight before aqueous treatment. Normal workup with removal of the organic solvent on a rotary evaporator at room temp and 40 mm press gave the various product mixtures. Vapor phase chromatograms were integrated (Table 1) and individual peaks collected and identified: *1-Chloro-2-pentanone* (**6**):[9] retention time 7·5 min; n_D^{16} 1·4386; 2·4 DNP m.p. 138–139° (lit.[9] 138°); NMR δ 0·93 (t, 3, H-5), 1·35–1·90 (m, 2, H-4), 2·57 (t, 2, H-3), 4·04 (s, 2, H-1); IR ($CHCl_3$) 2985 (s), 1730 cm^{-1} (s). *3-Chloro-2-pentanone* (**7**):[9] retention time 5·5 min; NMR δ 1·03 (t, 3, H-5), 1·7–2·2 (m, 2, H-4), 2·32 (s, 3, H-1), 4·15 (t, 1, H-3); IR ($CHCl_3$) 2985 (s), 1725 cm^{-1} (s). *1,1-Dichloro-2-pentanone* (**8**):[10] retention time 10·5 min; n_D^{22} 1·4483 (lit.[10] 1·4478); NMR δ 0·97 (t, 3, H-5), 1·4–2·0 (m, 2, H-4), 2·82 (t, 2, H-3), 5·80 (s, 1, H-1); IR ($CHCl_3$) 2290 (s), 1740 cm^{-1} (s). *1,1,1-Trichloro-2-pentanone* (**9**):[11] retention time 19·7 min; n_D^{20} 1·4615, (lit.[11] 1·4618); NMR δ 0·99 (t, 3, H-5), 1·4–2·0 (m, 2, H-4), 2·97 (t, 2, H-3); IR ($CHCl_3$) 2990 (s), 1760 cm^{-1} (s).

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