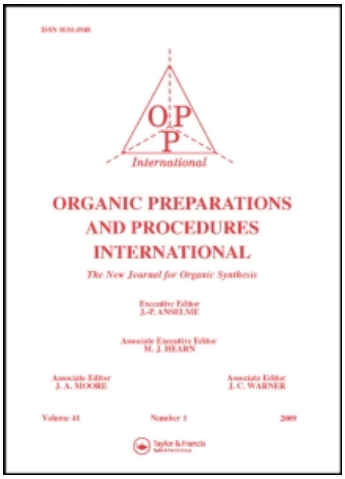

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A SIMPLE ROUTE TO SOME SPIROIMIDAZOLONES

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7. Although the yields reported were for alkyl bromides, the reaction works well with alkyl chlorides. Alkyl iodides give the best yields.

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A SIMPLE ROUTE TO SOME SPIROIMIDAZOLONES

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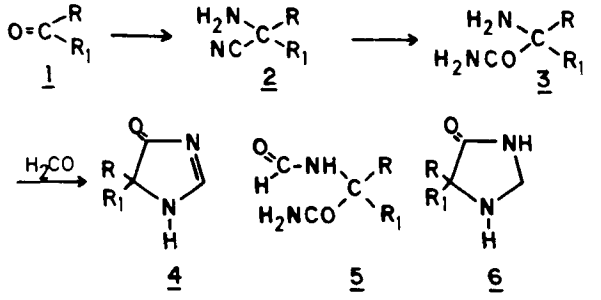
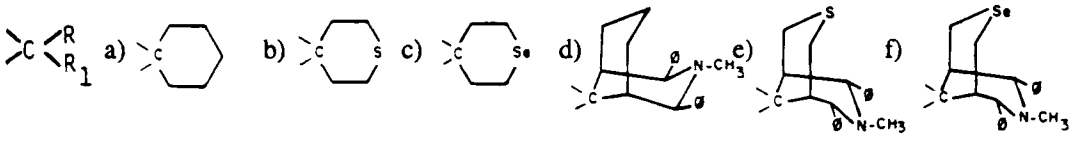
Although the synthesis of imidazoles is relatively well-known reaction,[1] the yields are low. One such approach for the preparation of spiroimidazoles (4) involves reactions of aminocarboxamides (3) with ethyl orthoformate at reflux for several days;[2] often the non-cyclic intermediate (5) was obtained in the mixture together with the desired spiroimidazolone. In this context, we have developed a simple method for synthesis of spiroimidazolones using gaseous formaldehyde in the cyclization. Under these conditions and working at room temperature, the reaction time was shortened. Treatment of the aminocarboxamides (3)[3,4] (from the aminonitriles 2)[5] with a high concentration of formaldehyde made extraction of the product unnecessary since the products (4) precipitated as solids by addition of water and basification with ammonium hydroxide. Recrystallization provided pure products as white or yellow needles. A maximun yield (by IR) was obtained after 20-30 min. in all reactions, irrespective of the aminocarboxamide employed. Unfortunately, preliminary experiments indicated that non-cyclic aminocarboxamides derived from diisopropyl ketone 3g (R = R_1 = $CHMe_2$), benzophenone 3h (R = R_1 = Ph) and acetophenone 3i (R = Me, R_1 = Ph) did not undergo the desired reaction, with gaseous

formaldehyde even after 24 hrs and starting materials were recovered. These imidazolones could be made by the reductive desulfurisation of the corresponding thiohydantoins.[6] The C=N streching vibrations at 1570-1550 cm^{-1} are consistent with a conjugated arrangement since this absorption would be shifted towards higher frequencies (1630 cm^{-1}) if they were in an unconjugated arrangement.[7]





The mode of oxidation step remains unknown. Catalytic hydrogenation on 5% Pd/C, readily converted these compounds to the spiroimidazolidinones (6),[8] as shown by the disappearance of the C=N streching vibration at 1560 cm^{-1}; their ^1H NMR spectra show peaks attributable to the N_1-H and N_3-H at 2.76 and 7.96 respectively, and C_2-H at 4.40,[9] recognizable by the integrated areas.

EXPERIMENTAL SECTION

The melting points were determined on a Kofler Block and are uncorrected. IR spectra were taken on a Perkin-Elmer 570 or 283 spectrophotometers. ^1H NMR spectra were recorded on a Hitachi-Perkin-Elmer R-24B spectrometer at 60 MHz in $CDCl_3$ using TMS as internal standard. Elemental analyses were performed on a Carlo-Erba 1106 or Perkin-Elmer 240. The starting ketones were commercial reagents (E. Merck) or prepared according to the literature.[10-14] The aminonitriles 2 were prepared by a modified Strecker synthesis.[5] The aminocarboxamides 3 were obtained by modification of a known method.[3]

General Synthetic Procedure for Aminonitriles (2).- Ketone 1 (8 mmol), potassium cyanide (8 mmol) and ammonium chloride (12 mmol) in dimethylformamide (60 ml) were placed in a 250 ml flask, and the reaction mixture was maintained at 60° for 4 days. The solution was poured into water (400 ml), the precipitated product was collected and was washed with diethyl ether (100 ml), dried and purified by recrystallization.

General Procedure for Synthesis of Aminocarboxamides (3).- A solution of the corresponding aminocarbonitrile (20 mmol) in conc. sulfuric acid (60 ml) was stirred at room temperature for 48 hrs. The mixture was then poured slowly with stirring into an

excess of ice and conc. ammonium hydroxide. The solid was collected, washed with water and dried. The crude product was crystallized.

TABLE 1. Spectral Data

Compd	IR(KBr) cm^{-1}	^{1}H-NMR($CDCl_3$,δ)
2b	3380, 2980, 2900, 2220	1.90(m, 2 H), 2.85(m, 2 H), 3.10(m, 2 H)
2c	3390, 2990, 2930, 2220	1.80(m, 2 H), 2.80(m, 2 H), 3.00(m, 2 H)
2d	3390, 3100, 2880, 2220	1.80-1.10(m, 8H), 1.90(s, 3 H), 2.05(m, 2 H), 4.30, 4.70(d, 2 H), 7.50-7.20(m, 10 H)
2e	3390, 2990, 2860, 2220	2.05(s, 3 H), 2.60-2.30(m, 8 H), 4.20(d, 2 H), 7.50-7.10(m, 10H)
2f	3390, 3000, 2970, 2210	2.00(s, 3 H), 2.80-2.50(m, 5 H), 3.60-3.40(m, 2H), 5.15-5.00(m, 2 H), 7.60-7.10(m, 10 H)
3b	3360, 3290, 2900, 1670	2.20(s, 2 H), 2.75(m, 2 H), 3.00(m, 2 H), 5.70(s, 2 H)
3c	3369, 3270, 2900, 1670	2.00(s, 2 H), 2.90(m, 2 H), 3.2(m, 2 H), 5.85(s, 2 H)
3d	3360, 3290, 2860, 1675	1.60-0.90(m, 8 H), 2.00(s, 3 H), 2.40-2.20(m, 2 H), 4.20(d, 2 H), 5.90(s, 2 H),7.40-7.10(m, 10 H)
3e	3360, 3290, 2790, 1660	2.00(s, 3 H), 2.40-2.10(m, 6 H), 3.30-3.10(m, 2 H), 3.60-3.40(m, 2 H), 4.40(d, 2 H), 7.40-7.00 (m, 10 H)
3f	3360, 3290, 3060, 1665	1.90(s, 3 H), 2.80-2.40(m, 6 H), 3.80-3.65(m, 2 H), 4.90-4.70(d, 2 H), 7.70-7.20(m, 10 H)
4b	3190, 2960, 1700, 1560	2.30(s, 1 H), 2.60(m, 2 H), 2.80(m, 2 H), 4.40(s, 1 H)
4c	3180, 2950, 1710, 1560	2.50(s, 1 H), 2.70(m, 2 H), 2.90(m, 2 H), 4.40(s, 1 H)
4d	3190, 2950, 1700, 1560	1.60-1.00(m, 7 H), 2.00(s, 3 H), 3.20(s, 2 H), 3.70(d, 2 H), 4.40(s, 1 H), 7.40-7.00(m, 10 H)
4e	3190, 2970, 1690, 1560	1.90(s, 3 H), 2.60-2.30(m, 4 H), 2.80(s, 1 H), 3.30-3.10(m, 2 H), 4.20-4.00(d, 2 H), 4.50(s, 1 H), 7.70-7.20(m, 10 H)
4f	3190, 2980, 1680, 1560	2.00(s, 3 H), 2.70-2.50(m, 4 H), 3.00(m, 1 H) 3.90-3.70(m, 2 H), 4.40(s, 1 H), 4.85-4.60(d, 2 H), 7.80-7.30(m, 10 H)

TABLE 2. Analytical Data

Compd	mp.(C°) (solvent)	Yield (%)	Anal. Calcd.(Found) C	H	N
2b	123-124 (MeOH)	65	50.67(50.61)	7.08(7.19)	19.69(19.62)
2c	116-117 (EtOH)	49	38.10(38.07)	5.33(5.38)	14.81(14.78)
2d	127-129 (MeOH)	25	79.71(79.69)	7.69(7.66)	12.67(12.57)
2e	143-145 (MeOH)	35	72.16(72.25)	6.63(6.75)	12.02(11.98)
2f	156-157 (EtOH)	23	63.62(63.56)	5.48(5.56)	10.60(10.55)
3b	110-111 (MeOH)	40	44.97(44.89)	7.53(7.57)	17.48(17.39)
3c	106-107 (MeOH)	56	34.79(34.73)	5.83(5.88)	13.52(13.51)
3d	200-201 (Me_2CO)	40	75.60(75.53)	7.78(7.89)	12.02(11.97)
3e	210-212 (Me_2CO)	49	68.62(68.77)	6.85(6.93)	11.43(11.37)
3f	217-219 (EtOH)	53	60.86(60.77)	6.08(6.01)	10.14(10.00)
4a	165-166 (EtOAc)	76		see ref. 2	
4b	128-129 (EtOH)	55	49.39(49.32)	5.92(5.99)	16.45(16.39)
4c	130-132 (EtOH)	45	38.72(38.68)	4.64(4.67)	12.90(12.86)
4d	120-122 (Et_2O-C_6H_{12})	65	76.84(76.60)	7.01(7.12)	11.69(11.76)
4e	146-148 (PhH-C_6H_{12})	78	69.99(69.88)	6.14(6.19)	11.13(11.18)
4f	151-152 (PhH)	70	62.25(62.30)	5.46(5.51)	9.90(9.89)

General Procedure for Synthesis of Imidazolones (4).- A 250 ml, three-necked flask was equipped with a condenser, a mechanical stirrer and glass tube; the assembled apparatus was protected from moisture by means of a drying tube. Gaseous formaldehyde may be obtained by placing an excess of paraformaldehyde (previously dried for 2 days over phosphorus pentoxide) in a round-bottomed flask provided with an inlet tube for admitting dry nitrogen. The flask is heated in an oil bath at 180-200° and the gaseous formaldehyde is carried into the reaction flask by a slow stream of nitrogen through glass tube (4 mm diameter) fitted into the neck of the flask; the entry tube should terminate about 1 cm above the surface of the solution. Thus, the gaseous formaldehyde was passed into a solution of aminocarboxamide (10 mmol) in dry dimethylformamide (50 ml) during the entire reaction time (20-30 min.). The cold mixture was treated with conc. ammonium hydroxide and the solid was collected by filtration, washed with water and dried. The crude product was recrystallized.

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