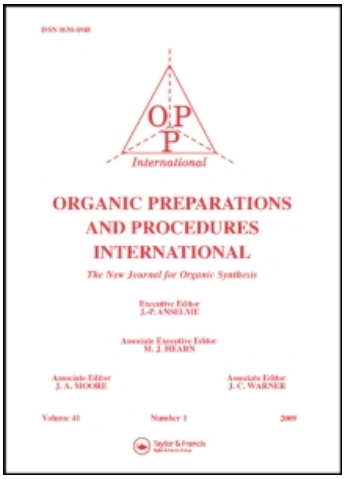

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SYNTHESIS AND ELECTROPHILIC SUBSTITUTION REACTIONS OF FLUORINE CONTAINING ARYLGLYOXAL 2-ARYLHYDRAZONES

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SYNTHESIS AND ELECTROPHILIC SUBSTITUTION REACTIONS OF FLUORINE CONTAINING ARYLGLYOXAL 2-ARYLHYDRAZONES

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(03/20/84)

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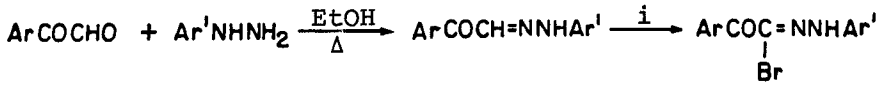
Recently, hydrazidoyl bromides (α-ketohydrazonyl halides) have aroused interest as versatile reaction intermediates for the synthesis of a variety of heterocyclic systems such as 1,4-dihydro-1,2,4,5-tetrazines, 4,5-dihydro-1H-pyrazoles, pyrazoles, 1,3,4-oxadiazolines and Δ^2-triazolines in already through 1,3-dipolar cycloaddition or nucleophilic substitution reactions.[1-4] A comprehensive survey of the available literature suggested further areas of investigation.[1,5]

We now report the bromination, chlorination and nitration reactions of arylglyoxal 2-arylhydrazones (III) under controlled conditions.

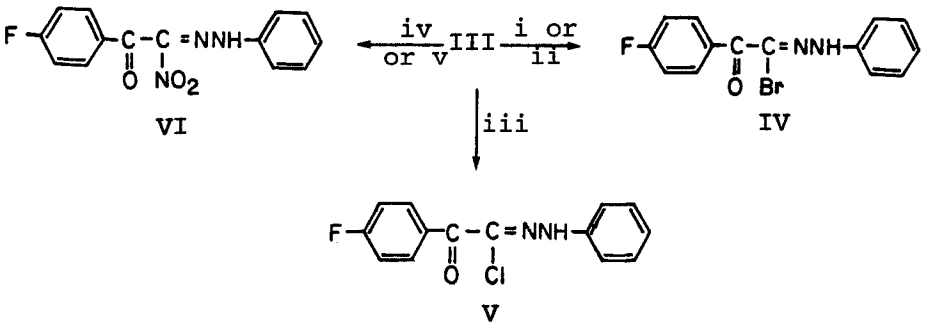
EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 157G spectrophotometer as KBr pellets. ^{1}H NMR specra were obtained on Bruker HX-90 using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on Kratos 30 and/or 50.



I II III IV

a) Ar = 4-FC_6H_4, Ar^1 = C_6H_5
b) Ar = 4-F-2-$CH_3C_6H_3$, Ar^1 = C_6H_5
c) Ar = 2-Cl-4-FC_6H_3, Ar^1 = C_6H_5
d) Ar = 2-F-5-$CH_3C_6H_3$, Ar^1 = 2,4-$(NO_2)_2C_6H_3$
e) Ar = 4-F-2-C_6H_3, Ar^1 = 2,4-$(NO_2)_2C_6H_3$
f) Ar = 2-Cl-4-FC_6H_3, Ar^1 = 2,4-$(NO_2)_2C_6H_3$
g) Ar = 4-FC_6H_4, Ar^1 = C_6H_5
h) Ar = 4-F-2-$CH_3C_6H_3$, Ar^1 = C_6F_5



VI IV V

i) Br_2-AcOH ii) NBS-CCl_4 iii) NCS-CCl_4
iv) $Cu(NO_3)_2 \cdot 3H_2O$-Ac_2O v) Fum. HNO_3-Conc. H_2SO_4(1:1)-Ether

4-Fluorophenylglyoxal 2-phenylhydrazone(III). Typical Procedure.- 4-Fluorophenylglyoxal (1.5 g, 0.01 mol) was treated with phenylhydrazine (1.0 g, 0.01 mol) in ethanol (25 ml) and refluxed for 5 hrs. On cooling, the hydrazone separated as yellow orange crystals, which were collected and recrystallized from methanol to provide 1.1 g (75%) of IIIa, mp. 125°. IR(KBr): 3200-3240, 1640, 1610-1600 cm^{-1}; ^1H NMR($CDCl_3$): δ 11.5 (s, 1H, NH), 7.0-7.2 (s, 1H, -CH=C), 7.2-8.5 (m, 9H, Ar); MS: m/e 242 (M^+).

Anal. Calcd for $C_{14}H_{11}FN_2O$: C, 69.42, H, 4.54, N, 11.35
Found: C, 69.20, H, 4.44, N, 11.57

Analytical and spectral data for all of the compounds (IIIb-IIIh) which were

synthesized by the above procedure are recorded in Table 1.

4-Fluorophenylglyoxal 2-bromo-2-phenylhydrazone(IVa). Typical Procedure.- 4-Fluorophenylglyoxal 2-phenylhydrazone (2.4 g, 0.01 mol) was rapidly stirred in glacial acetic acid (70 ml) at room temperature, while a solution of bromine (1.6 g, 0.01 mol) in acetic acid (20 ml) was added dropwise during 30 min. The bromo derivative was collected after 5 hrs, washed thoroughly with water and recrystallized from acetic acid to provide 1.8 g (75%) of IVa, mp. 180°.

IR(KBr): 3240, 1650, 1600 cm^{-1}, ^1H NMR($CDCl_3$): δ 10.8 (s, 1H, NH), 7.2-8.5 (m, 9H, Ar), MS: m/e 321 (M^+).

Anal. Calcd for $C_{14}H_{10}BrFN_2O$: C, 52.33; H, 3.11; N, 8.72

Found: C, 52.21; H, 3.10; N, 8.69

Analytical and spectral data for all of the compounds (Vb-IVh) which were synthesized by the above procedure are recorded in Table 2.

IVa from N-Bromosuccinimide.- A mixture of 4-fluorophenylglyoxal 2-phenylhydrazone (2.4 g, 0.01 mol) and N-bromosuccinimide (4.5 g, 0.03 mol) was refluxed in dry carbon tetrachloride for 3 hrs. It was cooled to 0°, the succinimide formed removed by filtration and the filtrate repeatedly washed with water. It was then dried over anhydrous sodium sulphate, filtered and the solvent evaporated under reduced pressure. The solid thus obtained was recrystallized from ethanol (95%) to provide 1.5 g (65%) of IVa, mp. 179°. The product exhibited spectral (IR, NMR and MS) and analytical data identical to that of IVa obtained above.

4-Fluorophenylglyoxal 2-chloro-2-phenylhydrazone (V).- A mixture of 4-fluorophenylglyoxal 2-phenylhydrazone (2.4 g, 0.01 mol) and N-chlorosuccinimide (3.1 g, 0.03 mol) in dry carbon tetrachloride (40 ml) was refluxed for 3 hrs. The mixture was cooled to 0° and the succinimide which had precipitated was removed by filtration and the filtrate washed repeatedly

with water. It was then dried over anhydrous sodium sulphate, filtered and the solvent evaporated under reduced pressure. The solid was recrystallized from 95% ethanol, which gave a single spot on TLC plate using benzene as mobile phase. The yield of V, mp. 160° was 1.4 g (60%).

IR(KBr): 3250, 1640, 1600 cm^{-1}; ^1H NMR($CDCl_3$): δ 11.5 (s, 1H, NH), 7.5-8.5 (m, 9H, Ar).

Anal. Calcd for $C_{14}H_{10}ClFN_2O$: C, 60.75; H, 3.61; N, 10.16

Found: C, 60.72; H, 3.59; N, 10.06

4-Fluorophenylglyoxal 2-nitro-2-phenylhydrazone (VI).- A cooled solution of 4-fluorophenylglyoxal 2-phenylhydrazone (2.4 g, 0.01 mol) in acetic anhydride (5 ml) was added dropwise with constant stirring, to powdered cupric nitrate trihydrate 5.8 g (0.03 mol) in acetic anhydride 5 ml. The resultant mixture was kept at 0-5° for 10 hrs. and the bluish green solution, treated with an ice-cold solution of sodium acetate (8.2 g, 0.01 mol). The two phase liquid mixture was stirred for 5 hrs. during which time a finally divided greenish precipitate separated out. It was removed by filtration, washed with water and recrystallized from ethanol (95%). The product a gave single spot in TLC using benzene-pet. ether (2:1). The yield of VI, mp. 180°, was 65%.

IR(KBr): 3240, 1640, 1600, 1540 cm^{-1}, ^1H NMR($CDCl_3$): δ 8.8 (s, 1H, NH), 7.5-8.5 (m, 9H, Ar).

Anal. Calcd for $C_{14}H_{10}FN_3O_3$: C, 58.54; H, 3.48; N, 14.63

Found: C, 58.41; H, 3.45; N, 14.89

VI from Nitrating Mixture.- A suspension of the 4-fluorophenylglyoxal 2-phenylhydrazone (2.4 g, 0.01 mol) in ether 50 ml was stirred at room temperature and treated with the nitrating mixture (16 ml, 1:1 fuming HNO_3 and conc. H_2SO_4) dropwise over a period of 20 min. The stirring was continued for an additional 30 min. after which time the mixture was neutralized with

sodium carbonate solution, extracted with ether (3x50 ml) and the combined ethereal layer was washed with water, dried over anhydrous sodium sulphate.

Table 1. Arylglyoxal 2-Arylhydrazones (III)[a]

Compd. No.	mp. (°C)	Yield (%)	Elemental Analyses Calcd(Found) C	H	N
IIIb	145	80	70.31(70.19)	5.07(5.10)	10.93(11.20)
IIIc	118	78	60.75(60.60)	4.61(4.54)	10.13(10.21)
IIId	160	65	52.02(52.10)	3.17(3.14)	16.18(16.20)
IIIe	142	65	52.02(52.00)	3.17(3.14)	16.18(16.20)
IIIf	125	60	45.83(45.81)	2.18(2.15)	15.61(15.51)
IIIg	120	75	50.60(50.54)	1.80(1.78)	8.43(8.39)
IIIh	121	80	52.02(52.00)	2.31(2.29)	8.00(7.90)

a) IR(KBr): 3200(NH), 1660(C=O), 1600(C=N) cm^{-1}. ^1H NMR: δ 11.0-12.0(NH), 7.0-7.2(CH=C), 7.2-8.5 (ArH). MS: M^+[m/z, 256 (IIIb)].

Table 2. Arylglyoxal 2-Bromo-2-arylhydrazones (IV)[a]

Compd. No.	mp. (°C)	Yield (%)	Elemental Analyses Calcd (Found) C	H	N
IVb	190	80	53.53(53.71)	3.58(3.50)	8.35(8.37)
IVc	200	70	47.25(47.20)	2.53(2.51)	8.34(8.25)
IVd	210	65	43.58(43.54)	2.42(2.40)	13.17(13.19)
IVe	160	65	43.58(43.54)	2.42(2.40)	13.17(13.21)
IVf	180	68	39.11(39.10)	1.62(1.61)	12.56(12.60)
IVg	150	70	40.87(40.83)	1.21(1.19)	6.81(6.75)
IVh	150	68	42.35(42.21)	1.64(1.62)	6.58(6.60)

a) IR(KBr): 3250(NH), 1660(C=O), 1590(C=N) cm^{-1}. ^1H NMR($CDCl_3$): δ 10.8-11.1(NH), 7.2-8.0 (ArH), 7.8(NH) (IVg). MS: M^+[m/z, 335 (IIIb)].

The solvent was removed under reduced pressure to yield the crude product, which was purified by recrystallization from 95% ethanol to provide 1.6 g (68%) of VI, mp. 118^{1}°. The product was identical in all respects (spectral and analytical data, mp. and mixed mp.) with VI obtained from 4-fluoroglyoxal-2-phenylhydrazone and cupric nitrate trihydrate in acetic anhydride.

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