Reactions with Trifluoro-\(N\)-(4-nitrophenyl)acetohydrazonoyl Bromide: A New Route for the Synthesis of Fluorinated Polyfunctionally Substituted Pyrazoles, Thiadiazoles, Selenadiazoles and a Pyrrolo[3,4-\(d\)]pyrazole

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Trifluoro-\(N\)-(4-nitrophenyl)acetohydrazonoyl bromide (1) reacts with doubly activated methylene compounds to afford trifluoromethylpyrazole derivatives (2-7), with potassium selenocyanate and potassium thiocyanate (or thiourea) to afford 2-imino-3-\(p\)-nitrophenyl-5-trifluoromethyl-1,3,4-selenadiazole and its thiadiazole analogue (9a,9b respectively) and with \(N\)-phenylmaleimide to afford a pyrrolo[3,4-\(d\)]pyrazole-4,6-dione (13).

Hydrazonoyl halides are versatile reagents which have been extensively utilized in heterocyclic synthesis.1,2 However, very few publications have dealt with trifluoromethyl acetohydrazone halides.3-5 In continuation of our interest in the synthesis of pyrazole derivatives bearing a trifluoromethyl group,6-7 we report herein the synthesis of several new trifluoromethylpyrazole, trifluoromethylselenadiazole, thiadiazole and pyrrolo[3,4-\(d\)]pyrazole-4,6-dione derivatives required for a medicinal chemistry program. Heterocyclic compounds having a fluorine atom or trifluoromethyl group are of considerable interest on account of their excellent pharmacological activity.8,9

Results and Discussion

Treatment of trifluoro-\(N\)-(4-nitrophenyl)acetohydrazonoyl bromide (1) with dibenzoylmethane or acetoacetanilide in refluxing ethanolic sodium ethoxide afforded the pyrazole derivative 2 or 3, respectively (Scheme 1).

![Scheme 1](image)

It has been reported that hydrazonoyl halides react with doubly activated methylene compounds to provide a regioselective synthesis of pyrazole derivatives containing a variety of substituents in the 4- and 5-positions.1 Simlarly we now find that 1 reacts with the \(\beta\)-oxosulfones 4a-d to afford the 5-substituted 1-\(p\)-nitrophenyl-4-phenylsulfonyl-3-trifluoromethylpyrazoles 5a-d.

The reaction of 1 with malononitrile in refluxing ethanolic sodium ethoxide yielded 5-amino-4-cyano-1-\(p\)-nitrophenyl-3-trifluoromethylpyrazole (6), which was converted into the corresponding carboxamido derivative 7 upon treatment with sulfuric acid at room temperature. An authentic sample of 7 was prepared by treatment of 1 with cyanoacetamide in refluxing ethanol containing sodium ethoxide.

On the other hand, treatment of 1 with potassium selenocyanate or potassium thiocyanate (or thiourea), in refluxing ethanol, afforded compounds 9a,b, respectively (Scheme 2). The formation of 9 is assumed to proceed via a nucleophilic substitution of the cyanate anion to afford the non-isolable intermediate 8 which then undergoes intramolecular cyclization. Compound 9b was also obtained from the reaction of 1 with thiourea in refluxing ethanol via the formation of an intermediate 10 which readily cyclized with loss of ammonia. Compounds 9a,b were acylated to afford the \(N\)-acyl derivatives 11a-d.

![Scheme 2](image)

The reaction of 1 with \(N\)-phenylmaleimide in boiling toluene, containing an equimolar amount of triethylamine, afforded 1-\(p\)-nitrophenyl-5-phenyl-3-trifluoro-
methylpyrrolo[3,4-d]pyrazole-4,6-dione (13) (Scheme 2). The formation of 13 can be reasonably explained by the nitrite intermediate undergoing cyclodehydration to the double bond of the N-phenylmaleimide to afford 12, followed by spontaneous aromatization via dehydrogenation to give 13.

Experimental

M.p.s were determined on an Electrothermal melting point apparatus, IR spectra were recorded for KBr discs using a Perkin-Elmer Model 1430 Ratio Recording Spectrophotometer. 1H NMR spectra were obtained in [D₆]chloroform on a Varian Gemini 200 MHz spectrometer. Elemental analyses were carried out by the Microanalytical Centre at Cairo University. Mass spectra were obtained using a Hewlett-Packard Quadrupole mass detector model 5970 attached to a Hewlett-Packard gas chromatograph (model 5890 Series II) at NIST, USA. Compounds 1 and 4 were prepared as described.11

Reaction of 1 with Active Methylenic Compounds. General Procedure—Dibenzyloxymethane, acetonecyanamide, the β-oxoaldehyde 4a-d, malononitrile and cyanoacetamide (each 0.01 mol) were taken in absolute ethanol (15 mL) containing sodium (0.01 mol). To this solution was added a solution of 1 (0.01 mol) in absolute ethanol (15 mL). The mixture was then refluxed for 3 h and left to cool. The precipitate which formed was filtered off, washed with water and crystallized from ethanol to afford compounds 2, 3, 5a–d, 6 and 7, respectively (see Table 1).

Acetylation of Compounds 9a,b.—Acetylation. A solution of compound 9a or b (0.005 mol) in acetic anhydride (10 mL) was stirred, at room temperature, for 2 h. The formed precipitate was collected by filtration, washed with water and crystallized from ethanol to afford 11a,c respectively.

Benzylation. To a solution of 9a or b (0.005 mol) in pyridine (15 mL) was added benzyl chloride (0.005 mol). The reaction mixture was then heated under reflux for 3 h, cooled, poured into ice-water and then acidified with HCl. The so-formed solid was filtered off, washed with water and crystallized from ethanol to afford 11b,d, respectively.

1-p-Nitrosophenyl-3-phenyl-3-trifluoromethylpyrrolo[3,4-d]pyrazole-4,6-dione (13)—Compound 1 (0.01 mol) was added to a solution of N-phenylmaleimide (0.01 mol) in toluene (30 mL) containing an equimolecular amount of triethylamine. The reaction mixture was then heated under reflux for 5 h and the solvent evaporated in vacuo. The residue was triturated with light petroleum (bp: 60–80°C) and the so-formed solid was collected and crystallized from ethanol.