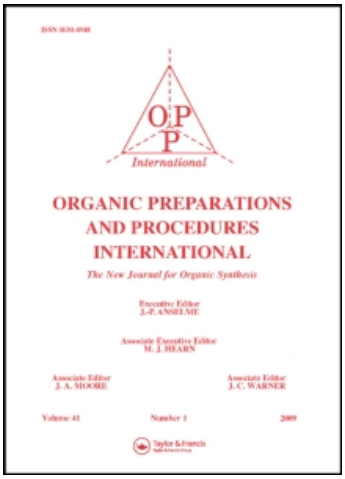

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INDIRECT IODINATION WITH 2-(3,5-DIIODO-4-METHOXYPHENYL)-1,3,4-OXADIAZOLE AS A PRECURSOR OF AN AROYL HYDRAZINE

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chloride (40 ml). A saturated sodium chloride solution (30 ml) was added to the CH_2Cl_2 extracts. The sodium chloride solution was then reextracted twice with methylene chloride (40 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the crude sulfone. Analysis by TLC and NMR confirmed that the sulfide had been consumed. The known sulfones were purified by vacuum distillation or recrystallization and characterized by NMR and IR. The percent yields and physical properties are reported in Table 1.

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INDIRECT IODINATION WITH 2-(3,5-DIIODO-4-METHOXYPHENYL)-1,3,4-OXADIAZOLE AS A PRECURSOR OF AN AROYL HYDRAZINE

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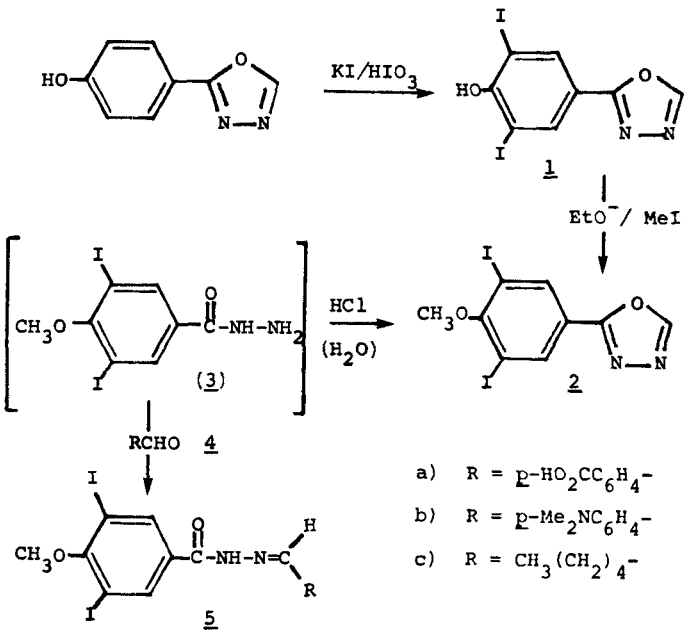
Iodinated contrast enhancement agents are frequently used to add

opacity to proximal tissues under radiographic scrutiny by computed tomography.[1] Hydroxyl groups on carrier molecules such as cholesterol or androgenic steroids have been used to attach iodinated benzoic acids and the resultant esters employed to enhance the contrast in tissues bearing steroidal receptors.[2] No convenient iodinated prosthetic group has been found for attachment at the carbonyl function of site-directed biomolecules.

We now report a facile route to an iodinated benzoic acid hydrazide (3) suitable for this purpose. Earlier work demonstrated that halogens ortho to phenolic hydroxyls rapidly deiodinate in vivo[3] but this does not appear to be the case with ortho-halogenated anisoles.[4]



Direct iodination of N-H containing molecules has, however, often been thwarted by apparent oxidative side-reactions.[5,6] These problems have been solved by the use of 3,5-diiodo-4-methoxybenzhydrazide (3) which, however, was unobtainable by direct electrophilic iodinations (ICl or KI, HIO_3) of either 4-hydroxyl- or 4-methoxybenzhydrazide. The N-H

functionalities of the hydrazide were therefore protected as a 1,3,4-oxadiazole, but even in this case iodination of 2-(4-methoxyphenyl)-1,3,4-oxadiazole gave only modest yields of 2. On the other hand, 2-(4-hydroxyphenyl)-1,3,4-oxadiazole could be iodinated in 66% yield and methylated in 77% yield to give 2. This oxadiazole serves as a shelf-stable, one-step precursor of 3,5-diiodo-4-methoxybenzhydrazide (3) which was generated and trapped *in situ* with carbonyl compounds to produce the hydrazones (5a-c) in 61-74% yields.

EXPERIMENTAL SECTION

NMR spectra were recorded on a JEOL-FX90Q instrument with TMS internal standard. IR spectra were determined on a Perkin-Elmer 283 spectrometer. Elemental analyses were performed by the Robertson Microanalytical Laboratory, Florham Park, NJ.

2-(3,5-Diiodo-4-hydroxyphenyl)-1,3,4-oxadiazole (1).- A solution of 10.0 g (62.0 mmol) of 2-(4-hydroxyphenyl)-1,3,4-oxadiazole,[7] 10.3 g (62.0 mmol) of potassium iodide, 93 ml of 2N acetic acid (186 mmol), 40 ml of water and 76 ml of ethanol was refluxed with vigorous magnetic stirring for 15 min. Iodic acid (6.5 g, 37.0 mmol) in 50 ml of water was added over 0.5 hr, the mixture was stirred at reflux for 1 hr, and additional potassium iodide (10.3 g, 62.0 mmol in 40 ml of water) was added over a period of 15 min. After 1 hr of reflux, the solution was evaporated *in vacuo* to ca. one-fourth of its volume, chilled in an ice-water bath and the precipitated product collected and recrystallized from dioxane:water (1:2) to yield 17.0 g (66%) of 1, mp. 198-200°; IR: 3140 cm^{-1} (OH); nmr (DMSO-d_6): δ 8.28 (s, 2, ArH), 9.29 (s, 1, oxadiazole C_5-H), and 10.28 ppm (br s, 1, OH).

Anal. Calcd. for $C_8H_4I_2N_2O_2$: C, 23.21; H, 0.97; N, 6.76

Found: C, 23.40; H, 1.08; N, 6.57

2-(3,5-Diiodo-4-methoxyphenyl)-1,3,4-oxadiazole (2).- To a well-stirred suspension of 9.9 g (24.0 mmol), of 1, 1.84 g (27.0 mmol) of sodium

ethoxide, and 80 ml of ethanol:tetrahydrofuran (1:1) at reflux was added dropwise 5.68 g (40 mmol) of methyl iodide over a period of 15 min. The mixture was refluxed for 1 hr, 4.54 g (32 mmol) of methyl iodide added, and reflux continued for 2 hrs. After concentration to one-half volume in vacuo, the mixture was poured over chopped ice and the solid collected. Analytically pure material (7.9 g, 77% yield) was obtained by recrystallization from tetrahydrofuran-water (1:2), mp. 164-166°; nmr (DMSO-d_6): δ 3.81 (s, 3, OCH_3) 8.36 (s, 2, ArH), and 9.36 ppm (s, 1, oxadiazole C_5-H).

Anal. Calcd. for $C_9H_6I_2N_2O_2$: C, 25.25; H, 1.41; N, 6.55

Found: C, 25.14; H, 1.31; N, 6.28

Preparation of Hydrazones. General Procedure.- Hydrazones could be prepared in one-step by in situ hydrolysis of 2 and trapping of carbonyl components in the same reaction vessel or by isolation of the intermediate 3 and subsequent condensation with the aldehydes in a second step. Differences in overall yield were negligible. A solution of 6.0 g (14 mmol) of 2-(3,5-diiodo-4-methoxyphenyl)-1,3,4-oxadiazole (2), 4.0 ml of conc. hydrochloric acid and 125 ml of tetrahydrofuran was refluxed for 3.5 hrs and evaporated to dryness in vacuo.

If at this point the residue was dissolved in 80 ml of water:THF (1:1), neutralized with conc. aqueous ammonia, reevaporated to dryness and recrystallized from water:THF (1:1), an 82% yield of analytically pure 3 could be obtained, mp. 191-192°; IR 3305/3200 (NH), 1630 cm^{-1} (C=O); nmr (DMSO-d_6): δ 3.74 (s, 3, OCH_3), 4.49 (br s, 2, NH_2), 8.21 (s, 2, Ar-H), and 9.81 (br s, 1, CONH).

Anal. Calcd. for $C_8H_8I_2N_2O_2$: C, 22.99; H, 1.93; N, 6.70

Found: C, 23.26; H, 2.08; N, 6.63

This isolation procedure, however, was superfluous since the crude

hydrazide itself could be used directly in the syntheses of hydrazones (5a-c) by addition of 14 mmol of aldehyde (4a-c), 150 ml of ethanol:THF (1:1) and 1 ml of glacial acetic acid to the dry unpurified hydrazide residue. After 2 hrs of reflux with vigorous stirring, the mixture was evaporated to dryness and the hydrazones recrystallized to analytical purity as described below.

3,5-Diiodo-4-methoxybenzoyl-(4-carboxyphenyl)hydrazone (5a) obtained in 74% yield, mp. 272-273° (from THF), by the direct combination of 2 and 4a.

Anal. Calcd. for $C_{16}H_{12}I_2N_2O$: C, 34.93; H, 2.20; N, 5.09

Found: C, 34.69; H, 2.42; N, 5.07

3,5-Diiodo-4-methoxybenzoyl-(4-N,N-dimethylaminophenyl)hydrazone (5b) obtained in 62% yield, mp. 182-183° from THF-hexane (1:3) by the direct combination of 2 and 4b.

Anal. Calcd. for $C_{17}H_{17}I_2N_3O_2$: C, 37.18, H, 3.12; N, 7.65

Found: C, 36.94; H, 3.16; N, 7.66

3,5-Diiodo-4-methoxybenzoyl-(n-pentyl)hydrazone (5c) obtained in 61% yield, mp. 183-185° [from THF:50-110° pet. ether (1:3)] by direct combination of 2 and 4c as described above.

Anal. Calcd. for $C_{13}H_{16}I_2N_2O_2$: C, 32.12; H, 3.32; N, 5.76

Found: C, 31.98; H, 3.24; N, 5.57

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A CONVENIENT SYNTHESIS OF N-5-(1,1-DIMETHYLETHYL)-3-ISOXAZOLYL-N,N-DIMETHYLUREA

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(11/05/84)

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A practical and economical synthesis of N-5-(1,1-dimethylethyl)-3-isoxazolyl-N,N-dimethylurea (4),[1] directly from pivalic acid without isolation of intermediates has been developed. This preparation offers the advantage that large scale reactions can be performed economically and efficiently