Synthesis and Electron Impact Mass Spectra of 3-Substituted 2-Acylaminoindazoles

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Dedicated to the memory of Professor Nicholas Alexandrou

3-Substituted-2-acylaminoindazoles **2** were prepared *via* oxidative cyclization of *o*-aminoaryl ketone acylhydrazones **1** with iodosobenzene diacetate. Their electron ionization mass spectra were recorded and in addition to the molecular ions show common fragmentation pathways corresponding to the $[M-N_2]^+$, $[M-NHCOX]^+$ and $[M-COX]^+$ ions, with some influence on the skeletal fragmentation by different substituents.

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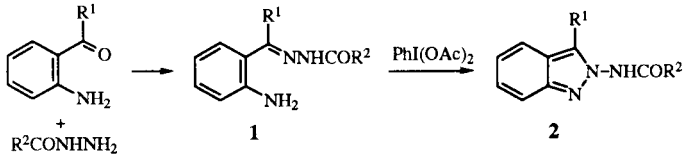
We have recently reported [1] the synthesis of 2-acylaminoindazoles *via* oxidative cyclization of *o*-aminoaryl ketone acylhydrazones on treatment with lead tetraacetate. This represents a simple two-step route from *o*-aminoaryl ketones and acylhydrazines to the relatively inaccessible 3-substituted-2-acylaminoindazole series.

A potential improvement to the procedure would involve substitution of the lead(IV) reagent with analogous but less hazardous and toxic oxidizing agents. The iodoso acetates, such as iodosobenzene diacetate, have received increasing attention as oxidants in organic synthesis [2,3], although with limited use for oxidations involving hydrazones. In the presence of iodosobenzene diacetate, benzophenone hydrazone was shown to couple with *N*-protected α-amino acids to give their diphenylmethyl esters [4] and aromatic aldehyde carbo-*t*-butoxyhydrazones were oxidizatively cyclized to 1,3,4-oxadiazolin-2-ones [5]. Recently, iodosobenzene diacetate was shown to be a suitable replacement for lead tetraacetate in both the oxidation of *o*-hydroxyaryl ketone acylhydrazones to give 1,2-diacylbenzenes [6] and diacetylresorcinol dibenzoylhydrazone to yield 1,3-diacetyl-2,4-dibenzoylbenzene [7].

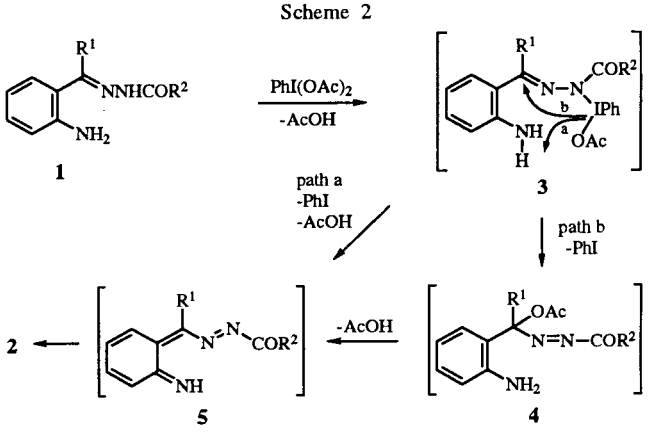
In the present work, the oxidative cyclization of *o*-aminoaryl ketone acylhydrazones **1** proceeded with iodosobenzene diacetate to afford 2-acylaminoindazoles **2** in comparable yields to those obtained using lead tetraacetate (Scheme 1). The proposed reaction pathway begins with ligand exchange by the *o*-amino ketone acylhydrazone **1** with an acetate group of the iodosobenzene diacetate to produce

Scheme 1



R^1, R^2 = a) Me, Ph b) Me, Me c) Me, *o*-HOC_6H_5 d) Ph, Ph e) Me, OEt f) Me, OBn

Scheme 2



intermediate **3** (Scheme 2). After reductive elimination of iodobenzene and another molecule of acetic acid *via* two alternative pathways involving intermediates **4** and **5**, cyclization to the 2-acylaminoindazoles **2** can occur. Intermediates **4** and **5** are common to the mechanism proposed for the oxidation with lead tetraacetate [1].

The 70 eV mass spectra of indazoles **2** are detailed in Table 1. The elemental composition of the fragment ions were confirmed by high-resolution mass spectra. The main fragmentation pathways of **2** are delineated in Scheme 3 using **2a** as a representative example, the mass spectrum of which is shown in Figure 1.

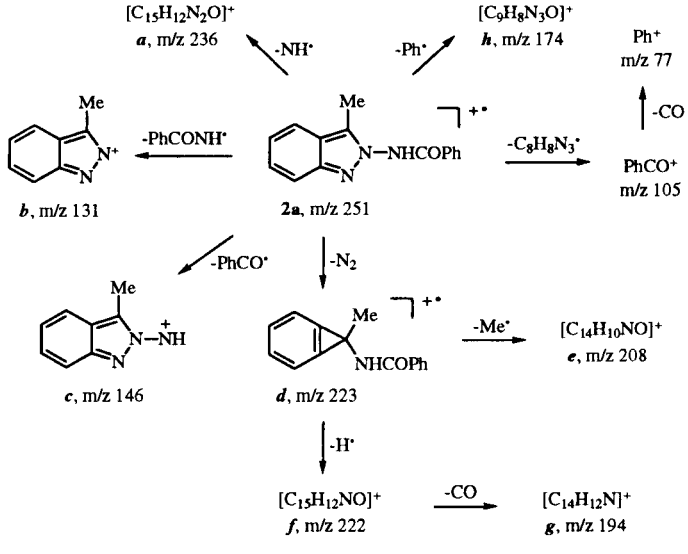
Peaks at m/z values corresponding to the molecular ions were prominent for the 2-acylaminoindazoles, with the exception of **2b**, indicating that they are fairly stable under electron impact conditions due to their aromatic character.

One fragmentation sequence involves the loss of a NH radical from the molecular ion to give rise to the ion *a* at m/z 236. A second pathway involves the loss of an NHCOPh radical to give the ion *b* at m/z 131. A third fragmentation leads to ion *c* at m/z 146 *via* loss of a PhCO radical from the molecular ion. Ions *b* and *c* are due to the scission of N-N and NH-CO bonds, respectively. These fragments are similar

Table 1
Fragment Ions in the Mass Spectra of 2-Acylaminoindazoles **2**

Compound	m/z (relative intensity)
2a	251 (30) M+, 236 (2), 223 (3), 232 (2), 222 (4), 209 (2), 208 (13), 194 (2), 180 (2), 174 (0.5), 146 (6), 131 (10), 105 (100), 77 (53)
2b	189 (1) M+, 174 (1), 161 (0.5), 160 (0.5), 147 (2), 146 (2), 132 (100), 118 (1)
2c	267 (67) M+, 252 (0.5), 239 (0.5), 238 (1), 225 (0.5), 224 (3), 210 (2), 196 (2), 174 (1), 146 (4), 131 (32), 121 (84), 93 (20)
2d	313 (47) M+, 298 (1), 285 (8), 284 (6), 256 (39), 236 (1), 208 (9), 193 (3), 105 (100), 77 (78)
2e	219 (100) M+, 160 (0.5), 146 (18), 145 (0.3), 131 (80), 77, (20)
2f	281 (28) M+, 237 (1.5), 190 (3.5), 174 (0.5), 146 (11.5), 132 (10), 131 (4), 91 (100), 77 (8)

Scheme 3



to the fragmentation pattern of carbonylhydrazones [8,9]. No similarities were found with indazole itself which isomerizes to *o*-cyanoaniline prior to fragmentation [10], a route not available to 3-substituted indazoles.

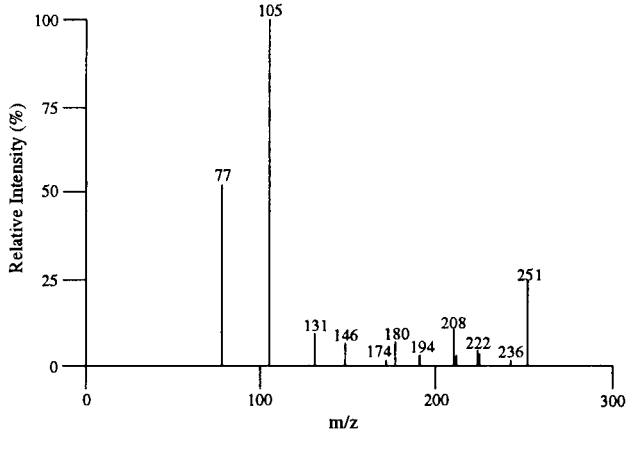


Figure 1. The 70 eV mass spectrum of 3-methyl-2-benzoylaminoindazole (**2a**).

A fourth fragmentation route proceeds *via* initial loss of N_2 from the molecular ion to give ion *d* at m/z 223. An analogous extrusion of N_2 with ring contraction to a three membered ring was observed in the mass spectra of pyrazole and indazolones [11]. It appears that the substituents at the 2-acylamino position influence the skeletal fragmentation since for carbamates **2e** (R^2 = OEt) and **2f** (R^2 = OBn) no loss of N_2 was evident.

Furthermore, loss of Me or H radicals from ion *d* gives rise to the ions *e* and *f*, respectively. Subsequently, loss of a CO molecule from the ion *f* leads to the formation of the ion *g* at m/z 194. A fifth fragmentation route proceeds *via* elimination of a Ph radical directly from the molecular ion and gives rise to the ion *h* at m/z 174.

EXPERIMENTAL

Low and high-resolution mass spectra were recorded on Finnigan MAT 4500 and Kratos MS-50 spectrometers respectively, with a 70 eV ionization energy and source temperatures in the range of 150-300°. All samples were introduced into the ion source through a direct insertion probe.

o-Aminoaryl ketone acylhydrazones **1** were prepared according to the literature method [1].

3-Substituted-2-Acylaminoindazoles **2a-f**.

General Procedure.

Iodosobenzene diacetate (0.64 g, 2 mmoles) is added gradually to a solution of the hydrazone **1** (1 mmole) in dichloromethane (10 ml) and the mixture is stirred at room temperature for 2 hours. After evaporation of the solvent, the crude product was washed with hexane, the hexane decanted off, and the remaining oil subjected to column chromatography (silica gel 70-230 ASTM) eluting with petroleum ether/ether (1:1, v/v) to give 2-acylaminoindazoles **2a-2f** in 69, 61, 74, 55, 78, and 79% yields, respectively. Indazoles **2** were identified by comparison of their spectral data with those reported in the literature [1].

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