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3-OXO-INDAZOLINE AND 4-OXO-DIHYDROQUINAZOLINE DERIVATIVES FROM ISATIC ACIDS

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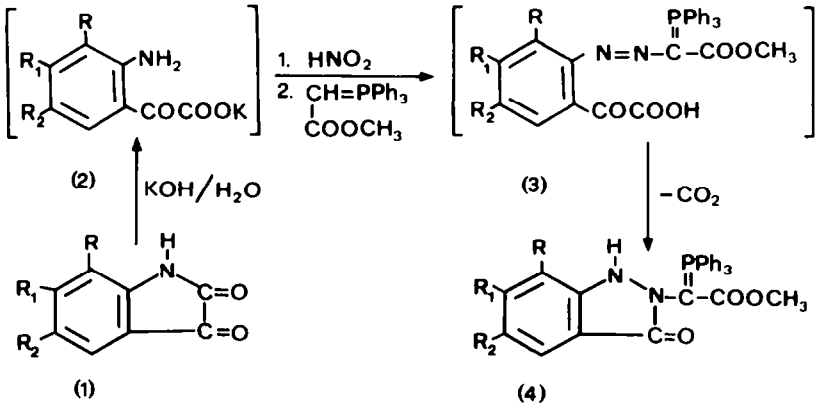
Abstract: The coupling of diazonium salts from isatic acids with alkoxycarbonylmethylenephosphoranes leads directly to 3-oxo-indazolin-2-yl-(alkoxycarbonyl)methylenetriphenylphosphoranes, while coupling with methyl 2-chloroacetacetate gives 2-[2-(methoxycarbonyl-chloromethyliden)hydrazino]-phenyl-glyoxylic acid.

Arylazomethylenetriphenylphosphoranes functionalized at the ortho position are suitable intermediates for the synthesis of heterocyclic compounds via inter- or intramolecular reactions[1]. Recently we reported that the coupling of diazonium ions from isatic acids (2) with methoxycarbonylmethylenetriphenylphosphorane (SCHEME 1) gave the 3-oxo-indazolin-2-yl-(methoxycarbonyl)methylenetriphenylphosphoranes (4a,b), instead of the expected (2-carboxycarbonylphenylazo)-(methoxycarbonyl)-methylenetriphenylphosphoranes (3a,b) that we needed as intermediates for the synthesis of cinnoline derivatives: in fact such a heterocyclic ring could, in principle, be obtained through an intramolecular Wittig reaction on the activated carbonyl group of compounds (3). With this goal in mind we investigated the above reactions

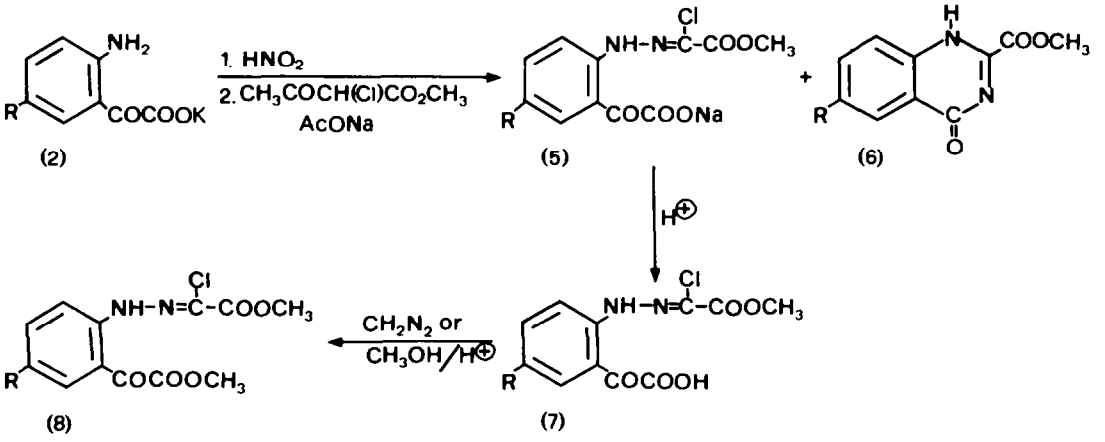
SCHEME 1



a: $R = R_1 = R_2 = H$ b: $R = R_1 = H$; $R_2 = Br$

further not only to see whether compounds (3) were intermediates in the formation of (4) but also if it was possible to isolate them and to address their reactivity towards the intramolecular Wittig reaction. Accordingly we tried to prepare (3a,b) from hydrazonoyl chlorides, PPh_3 and a base[2]. Diazotization of the potassium salts of the isatic acids (2a,b) followed by the coupling of the corresponding diazonium ions with methyl 2-chloroacetacetate afforded the hydrazonoyl chlorides (7a,b)(SCHEME 2). They were actually isolated as sodium salts (5): in the case of (2a) a small quantity of the 4-oxo-dihydroquinazoline derivative (6a) was also obtained.

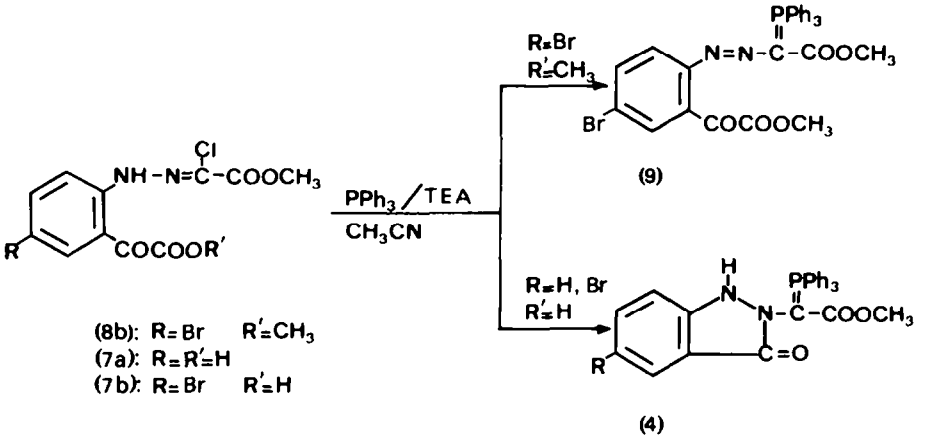
SCHEME 2



a: R = H b: R = Br

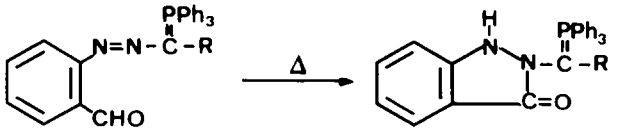
The structure of compound (6a) was demonstrated by comparing analytical and spectroscopical data with those of an authentic sample[3]. Prolonged digestion of (5) with diluted hydrochloric acid gave the corresponding acid derivatives (7): (7a) was identified as acid, while (7b) was characterized and identified through its methyl ester (8b), which was obtained by treating (7b) with diazomethane or by boiling it with a hydrochloric acid saturated methanol solution. The hydrazonoyl chlorides (7a,b) were reacted with PPh_3 and Et_3N at room temperature so as to obtain the azophosphoranes (3a,b), however the isolated products were the 3-oxo-indazolin-2-yl-methylenephosphoranes (4a,b)(SCHEME 3). The same reaction with the ester derivative (8b)

SCHEME 3



gave the expected arylazomethylenetriphenylphosphorane (9). These results show that: i) phosphoranes (3) are likely intermediates in the formation of the 3-oxo-indazolinyl derivatives (4); ii) phosphoranes (3) are highly reactive not isolable compounds which, upon formation, undergo immediate intramolecular cyclization in very different media (SCHEMES 1 or 3) and in mild conditions; iii) the esterification of the COCOOH function makes phosphorane (9) stable and isolable; iv) the presence of the COCOOH function as free acid is necessary for the (3) (4) cyclization; in fact (9), when submitted to thermal treatment was not transformed into products (4) but gave different products[5].

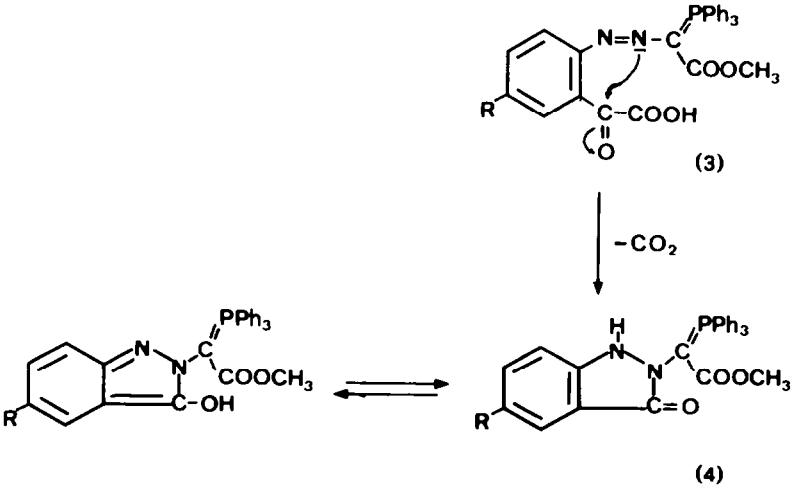
Moreover compounds such as o-formylarylazomethylenetriphenylphosphoranes (10), which can be thought to arise from decarboxylation of the corresponding glyoxylic acids (3), cannot be intermediates in the (3) (4)transformation. In fact, this reaction occurs spontaneously at room temperature, whereas structures (10) require higher temperatures to be transformed into the corresponding 3-oxo-indazolin-2-yl-methylenephosphoranes (4)[1].



(10) (4)

As a consequence of the above considerations one can imagine that the formation of compounds (4) occurs through the intramolecular nucleophilic attack of the -N=N- group on the highly reactive carbonyl group of compounds (3) and that decarboxylation would give (4)(SCHEME 4).

SCHEME 4



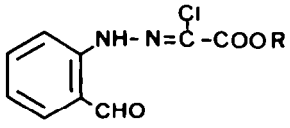
(3)

(4)

This mechanism is in line with our recent findings on the behaviour of azophosphoranes. In these compounds in fact, the -N=N- group has shown a great propensity to react as a nucleophile[4,5]. Particularly, it is able to give intramolecular nucleophilic attack on electrodeficient carbon atoms located in the ortho position on the aromatic ring[1,6].

Finally, as far as the formation of 4-oxo-dihydroquinazoline derivative (6a) is concerned, (SCHEME 2) we found that such a compound can be obtained also by the action of bases, even as weak as CH_3COONa, on hydrazonoyl chlorides (5a) or (7a). Analogously (7b) gave (6b).

Although several kinds of reaction paths can be imagined for this reaction, at the moment we have no proof of them. It is perhaps note worthy again that we have found that o-formylarylhydrazonoyl chlorides (11) are stable in the presence of bases and do not undergo cyclization to 4-oxo-dihydroquinazolines. This cyclization then appears as a peculiar feature of the behaviour of arylglyoxylic acid derivatives (7).



(11)

EXPERIMENTAL

M.p. were taken with a Büchi apparatus and are uncorrected. IR spectra were recorded by a Perkin-Elmer X98 spectrophotometer. ^1H NMR spectra were taken at 90 MHz with a Varian EM-390 spectrometer. Chemical shifts are expressed as δ values ($SiMe_4$ as internal standard). Mass spectra were taken with a Varian MAT 311-A spectrometer equipped with a combined E.I.-F.I.-F.D. ion source.

Silica gel (Merck, 70-230 mesh) was used for column chromatography. T.l.c.s were performed on Merck precoated silica gel 60F-254 plates.

Hydrazonoyl chlorides (7a,b)

The appropriate isatin (1a,b) (7.10^{-3} moles) was added in small portions to a solution of KOH (7.10^{-3} moles) in 10 cm^3 of water and the mixture was stirred at room temperature until a yellow solution was formed. To this solution kept at -3°C, $NaNO_2$ ($14\ 10^{-3}$ moles) in H_2O (4 cm^3) and EtOH (0.5 cm^3) was then added and the resulting cold mixture was dropped in 10 min into 20% H_2SO_4 ($31\ 10^{-3}$ moles), kept at -5°C. The thus obtained diazonium salt solution was added, in 15 min, at -5°C, to a stirred mixture of methyl 2-chloroacetoacetate ($7.7\ 10^{-3}$ moles), NaOAc(5g), MeOH(3cm^3). NaOAc(7g) was then added in small portions, so as to bring the pH to 4-5. The reaction mixture was kept at 0°C for 1 h and then at room temperature overnight. The sodium salt (5b) was filtered off, washed with iPrOH-$(iPr)_2O$ 2:1 (30 cm^3) and slurried with 5% HCl (20 cm^3) and left stirring overnight. The precipitate was filtered and washed with water to give 2,3 g of crude acid (7b). For identification and characterization purposes a small sample was transformed into the corresponding methyl ester by treating with CH_2N_2 (see below).

To recover the sodium salt (5a), insoluble in water and $CHCl_3$, the reaction mixture from (1a) was treated with $CHCl_3$ and then filtered. The precipitate (5a) was slurried with 5% HCl and afforded as the solid product practically pure (7a) in 9% yield. Quinazolinone (6a) was recovered in 10% yield from the $CHCl_3$ extract, after solvent evaporation and crystallization of the residue with EtOAc.

(5a) M.p. 163-164°C; ν_{max} (cm^{-1},nujol): 1740,1710 ^1H NMR (d_6-DMSO): 3.9(3H,s,OCH_3), 7.2(1H,broad s,NH), 7.6-7.9 (3H,m,aromatics),11.9(1H,s,COOH); Mass spectrum: m/z 283.5 (M^+). Analysis: found %: C=46.21, H=3.11, N=9.66; for $C_{11}H_8ClN_2Os$ calctd %: C=46.40, H=3.16, N=9.84

3-Oxo-indazolin-2-yl(methoxycarbonyl)methylenetriphenylphosphoranes (4)

a) From isatic acids by diazotization and coupling with methoxycarbonylmethylenetriphenylphosphorane.

General Procedure
To a solution of KOH ($2.4\ 10^{-2}$ moles) in H_2O (60 cm^3) the appropriate isatin (1a,c) ($2.04\ 10^{-2}$ moles) was added in small portions. The mixture was stirred at room temperature to a bright yellow coloured solution and eventually filtered. $NaNO_2$ ($2.55\ 10^{-2}$ moles) was tnen added and the obtained solution, cooled in an ice bath was then dropped, in 20 min. into 20% H_2SO_4 ($6.87\ 10^{-2}$ moles) kept at 0°C. The resulting diazonium salt solution was added in 15 min. to a solution of methoxycarbonylmethylenetriphenylphosphorane ($2.28\ 10^{-2}$ moles) in MeOH (100 cm^3) at 0°C. 8% NaOH was added to bring the to pH 8-9 and the reaction mixture stirred 1h at room temperature and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The residue from (1a), washed with Et_2O, EtOAc and ice cold MeOH, gave (4a)[3] in 29% yield.

The mixtures from (1b,c) on column chromatography (eluants: C_6H_6/EtOAc/Et_3N 100:100:1, starting from (1b); C_6H_6/EtOAc in ratios from 2:1 to pure EtOAc starting from (1c)) gave (4b)[3] in 31% yield and (4c) in 8% yield, respectively.
(4c) M.p. 189-190°C (acetone + EtOH). ν_{max} (cm^{-1}, nujol): 1630 (broad); H ^{1}NMR ($CDCl_3$): 2.10(3H,d,6-CH_3), 2.24(3H,d,7-CH_3),3.3+3.57(3H,2s,OCH_3), 6.43-7.95(17H,aromatics+0.65H,NH), 8.43 (0.35H,s,NH); Mass spectrum m/z 494 (M+). Analysis: found %: C=72.50, H=5.70, N=5.52; for $C_{30}H_{27}N_2O_3P$ calctd%: C=72.87, H=5.42, N=5.67

b) From isatic acids through hydrazonoylchlorides (7a,b).

General procedure
Et_3N ($14.8\ 10^{-3}$ moles) was added to a mixture of the appropriate hydrazonoyl chloride (7a,b)(see below)($2.46\ 10^{-3}$ moles) and PPh_3 ($2.46\ 10^{-3}$ moles) in CH_3CN (30 cm^3). After 24 h stirring at room temperature the precipitated product was filtered. (4a) was purified by precipitation with light petroleum from CH_2Cl_2 (75% yield). (4b) was purified by column chromatography (florisil, eluant EtOAc) and washing the recovered product with Et_2O (62% yield).

5-Bromo-2-[2-(methoxycarbonyl-chloromethyliden)hydrazino]-phenyl-glyoxylic acid methyl ester (8b)

a) To a slurry of the raw acid (7b)(0.2 g) in Et_2O, a saturated Et_2O solution of CH_2N_2 was added in small portions, until a clear solution was obtained. The residue from solvent evaporation was purified by dissolving it in toluene at room temperature. After filtration of some solid impurities and solvent evaporation (8b) was recovered practically pure in 90% yield. M.p. 148-149°C (iPrOH); ν_{max} (cm^{-1}; nujol): 1730 ($COOCH_3$); ^{1}H NMR ($CDCl_3$): 3.95-4.05 (6H,2s,OCH_3),7.7-8(3H, m, aromatics); Mass spectrum: m/z 377.4 (M+). Analysis: found %: C=38.15, H=2.92, N=7.12; for $C_{12}H_{10}BrClN_2O_5$ calctd %: C=38.16, H=2.65, N=7.42.

b) 4 cm^3 of dry HCl saturated MeOH solution were added to a slurry of the crude sodium salt (5b) (2.3 g) in MeOH (140 cm^3). The mixture was refluxed under stirring for 4h. After cooling at room temperature 2 g of crude (7b) were recovered by filtration and purified by column chromatography (eluant EtOAc/light petroleum 1:1) to give 1.6 g of pure product.

6-bromo-2-methoxycarbonyl-4-oxo-dihydroquinazoline (6b)
A solution of NaOAc (2 g) in H_2O (10 cm^3) was added to a solution of the hydrazonoyl chloride (7b) (0.076 moles) in MeOH (5 cm^3). After 3h stirring at room temperature the practically pure (6b) (0.028 g) was collected by filtration. M.p. 230-232°C (AcOH)(lit. 230-232°C) . The mother liquor was acidified and extracted with EtOAc. From the organic layer, dried over Na_2SO_4, some starting material (0.031 g) was recovered by solvent evaporation.

(4-Bromo-2-carbomethoxycarbonyl)-phenylazo-(methoxycarbonyl)-methylenetriphenylphosphorane (9)
Et_3N ($9.5\ 10^{-3}$ moles) was added to a mixture of hydrazonoyl chloride (8b) ($6\ 10^{-3}$ moles) and PPh_3 ($6.3\ 10^{-3}$ moles) in CH_3CN (100 cm^3). After 4 h stirring at room temperature the solvent was evaporated at reduced pressure. Column chromatography of tne residue (eluant: EtOAc/light petroleum 3:2) gave (9) in 50% yield.

M.p. 109°C (from MeOH); ν_{max} (cm^{-1}; nujol): 1730, 1720, 1680; ^1H NMR ($CDCl_3$): 3.6(3H,s,OCH_3), 3.7(3H,s,OCH_3), 6.35(1H,d,J=8,aromatics), 7.1-7.7(17H,m,aromatics).
Analysis: found %: C=59.55, H=3.97, N=4.34; for $C_{30}H_{24}BrN_2O_5P$ calctd %: C=59.70, H=3.98, N=4.64.

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