Studies on Heterocyclic Chemistry; Part XVII[1]. A New Synthetic Method for 2-Aminoindazole Derivatives

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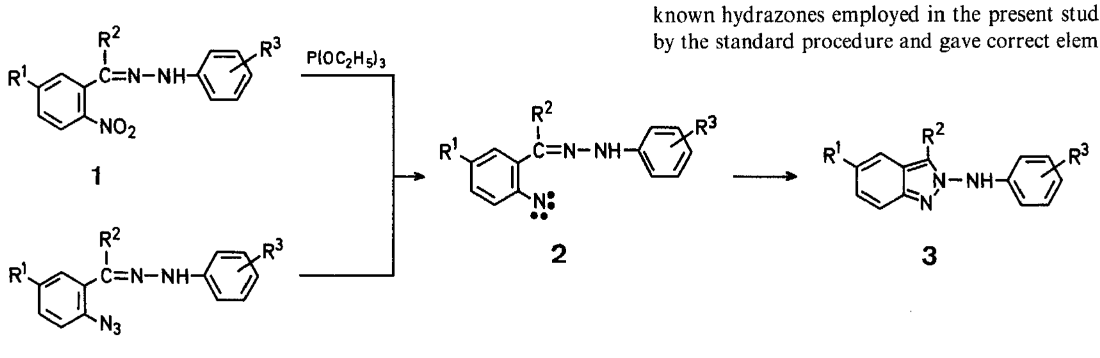
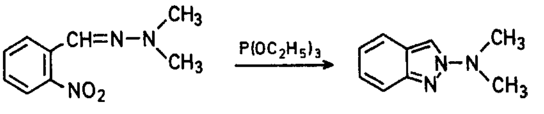
2-Aminoindazole derivatives have hitherto been prepared by the thermal decomposition of 2-azidobenzaldehyde hydrazone[2], the reaction of 6-nitroanthranil with phenylhydrazine[3], and the reaction of indazole with hydroxylamine-O-sulfonic acid[4]. The nitrene **2**, an intermediate in the thermal decomposition of 2-azidobenzaldehyde hydrazone to give 2-aminoindazole derivative **3**, could also be generated by the deoxygenation of 2-nitrobenzaldehyde hydrazone **1** with a tervalent phosphorus compound[5]. Nevertheless, Sakai and Anselme had failed to deoxygenate N-(2-nitrobenzylideneamino)-phthalimide to the corresponding indazole by this procedure[6]. According to our finding, the deoxygenation by triethyl phosphite can be successfully applied to the synthesis of 2-aminoindazole derivatives if there is no carbonyl group in the hydrazone substrate. The deoxygenation of 2-nitrobenzaldehyde arylhydrazones (**1**, $R^2 = H$) and of *o*-nitroacetophenone arylhydrazones (**1**, $R^2 = CH_3$) by triethyl phosphite proceed smoothly producing 2-arylaminoindazoles (**3**, $R^2 = H$) in moderate yield and 2-arylamino-3-methylindazoles (**3**, $R^2 = CH_3$) in low yield.

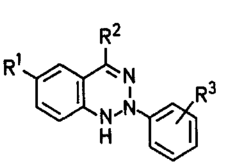


The reaction products were characterized by elemental analyses and spectrometric methods. The U.V. spectra listed in Table 1 show an absorption at 275–290 nm which is comparable to that reported for 2-substituted indazoles[7], whereas the I.R. spectra (Nujol) show an NH stretching absorption at 3200–3150 cm^{-1} and a band of moderate intensity at 1630 cm^{-1} characteristic of 2*H*-indazole derivatives[8]. The signal of 3-H appears in the lowest field ($\delta = 8.04$ for **3c**) in agreement with the N.M.R. spectral behaviour of indazole derivatives[9].



4 **5**

A further structural confirmation is derived from the reaction of 2-nitrobenzaldehyde dimethylhydrazone (**4**) with triethyl phosphite. If the foregoing product has the 1,2-dihydro-1,2,3-benzotriazine structure **6** which might be formed by the abstraction of an amino hydrogen by nitrene **2**, the deoxygenation of hydrazone **4** will afford a different type of product. However, the reaction proceeds smoothly and yields 2-dimethylaminoindazole (**5**) the U.V. spectrum of which is closely similar to those listed in Table 1. The deoxygenation of hydrazone **4** is complete within a few hours; 96% of the theoretical amount of triethyl phosphate was detected by G.L.C.



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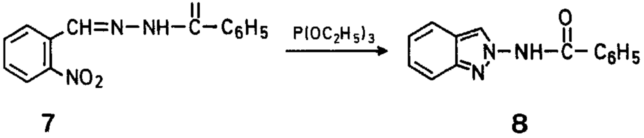
These observations prompted us to study the deoxygenation of 2-nitrobenzaldehyde benzoylhydrazone (**7**) with triethyl phosphite as a method for the synthesis of 2-aminoindazole itself[4]. However, 2-benzoylaminoindazole (**8**) was obtained in only 3% yield. This fact parallels the observation of Sakai and Anselme[6]; thus, we made no further attempt to find optimal reaction conditions.



7 **8**

The petroleum ether used was the fraction of b.p. 30-70°. Unknown hydrazones employed in the present study were prepared by the standard procedure and gave correct elemental analyses.

Table. 2-Arylaminoindazoles (**3**) from 2-Nitrobenzaldehyde Arylhydrazones (**1**) and Triethyl Phosphite

	R^1	R^2	R^3	Yield (%)	m.p.[a]	Elemental Analyses					U.V (C_2H_5OH) λ_{max} nm (ε)
3a	H	H	H	39	163–164°	$C_{13}H_{11}N_3$	calc.	C 74.62	H 5.30	N 20.08	277 (3.99)
							found	74.65	5.14	20.20	
3b	H	H	3-CH_3	52	144–146°	$C_{14}H_{13}N_3$	calc.	C 75.31	H 5.87	N 18.82	278 (4.01)
							found	75.10	5.62	18.61	
3c	H	H	4-CH_3	33	131–132°	$C_{14}H_{13}N_3$	calc.	C 75.31	H 5.87	N 18.82	278 (3.92)
							found	75.49	5.74	18.73	
3d	H	H	4-Cl	57	177–179°	$C_{13}H_{10}ClN_3$	calc.	C 64.07	H 4.14	N 17.25	237 (4.24), 279 (3.95)
							found	64.01	4.16	17.38	
3e	Cl	H	H	22	188–190°	$C_{13}H_{10}ClN_3$	calc.	C 64.07	H 4.14	N 17.25	280 (3.88), 300 (3.78)
							found	63.90	4.04	17.00	
3f	Cl	H	3-CH_3	34	157–159°	$C_{14}H_{12}ClN_3$	calc.	C 65.24	H 4.69	N 16.31	279 (3.97), 300 (3.87)
							found	65.33	4.57	16.21	
3g	H	CH_3	4-Cl	16	194–196°	$C_{14}H_{12}ClN_3$	calc.	C 65.24	H 4.69	N 16.31	236 (4.26), 290 (3.89)
							found	64.99	4.49	16.12	

[a] From benzene/petroleum ether.

Preparation of 2-Arylaminoindazoles (3); General Procedure:

A mixture of the 2-nitrobenzaldehyde arylhydrazone **1** ($R^2 = H$) or 2-nitroacetophenone arylhydrazone **1** ($R^2 = CH_3$) and triethyl phosphite (10 ~ 15 ml per 1.00 g of hydrazone) was heated at 160–170° for 10 hr under a nitrogen atmosphere. The excess of the phosphite was removed under reduced pressure and the residue was chromatographed on alumina. Benzene/ether (1:1) elution afforded the indazole **3**. Physical constant and U.V. spectral data are listed in Table 1.

2-Dimethylaminoindazole (5):

A mixture of 2-nitrobenzaldehyde dimethylhydrazone (**4**; 9.1 g) and triethyl phosphite (50 ml) was heated at reflux temperature for 5 hr under a nitrogen atmosphere. The excess of the phosphite was removed under reduced pressure and the residue was distilled in vacuo. G.L.C. analysis of the distillate revealed that the indazole was produced in 61% yield. Fractional distillation gave the indazole as a yellow oil; b.p. 99–104°/8 torr

$C_9H_{11}N_3$	calc.	67.05	6.88	N 26.07
	found	67.03	6.90	25.78

I.R. (film): $\nu_{max} = 1632\ cm^{-1}$.

U.V. (C_2H_5OH): $\lambda_{max} = 275$ nm ($\log \varepsilon = 4.02$).

^{1}H-N.M.R. (CCl_4): $\delta = 7.78$ (s, 1H), 7.60–6.83 (m, 4H), 2.95 (s, 6H).

2-Benzoylaminoindazole (8):

A mixture of 2-nitrobenzaldehyde benzoylhydrazone (**7**; 1.20 g) and triethyl phosphite (18 ml) was heated at reflux temperature for 4 hr under a nitrogen atmosphere. The excess of the phosphite was removed under reduced pressure and the residue was chromatographed on alumina. The indazole was eluted with methanol and crystallized from aqueous ethanol as needles; yield: 0.033 g (3%); m.p. 115–117°.

$C_{14}H_{11}N_3O \cdot 1/2\, H_2O$	calc.	C 68.28	H 4.91	N 17.07
	found	68.50	4.93	17.26

I.R. (Nujol): $\nu_{max} = 3180$ (NH), 1680 (C=O) cm^{-1}.

U.V. (C_2H_5OH): $\lambda_{max} = 277$ nm ($\log \varepsilon = 3.98$).

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