Tetrahedron Vol. 40, No. 15, pp 2983 to 2984, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00

NEW CONVENIENT ONE-STEP SYNTHESIS OF 4-ARYLPHTHALAZ-1-ONES

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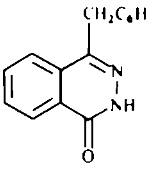
(*Received in UK* 5 *September* 1983)

Abstract—4-Arylphthalaz-1-ones (**2a–e**) are prepared by the hitherto unknown reaction of N-aminophthalimide (**1**) with aromatic hydrocarbons under Friedel–Crafts conditions. The reaction of N-aminophthalimide with Grignard reagents presents another convenient method for the synthesis of 4-alkyl or 4-arylphthalaz-1-ones.

The present investigation deals with a study of the hitherto unknown reaction of N-aminophthalimide (**1**) with aromatic hydrocarbons under Friedel–Crafts conditions. Thus, when N-aminophthalimide is allowed to react with aromatic hydrocarbons, namely, benzene, toluene, o-xylene, m-xylene or p-xylene in the presence of anhydrous aluminium chloride, good yields of 4-arylphthalaz-1-ones (**2a–e**), respectively are obtained. The reaction seems to proceed by arylation giving o-aroylbenzoic acid hydrazides (**3**) which loose water to give 4-arylphthalaz-1-ones (**2**). There is a possibility that this cyclisation is catalysed by the acidic reaction medium and is further accelerated by prolonged heat during the removal of excess hydrocarbon present in the reaction mixture by steam distillation. However, it was found that such prolonged heat is not necessary for cyclisation. This was shown by carrying out the reaction of N-aminophthalimide with toluene and the isolation of the organic layer by extraction with organic solvent to avoid steam distillation whereupon 4-(p-tolyl)phthalaz-1-one (**2b**) was also obtained in similar yield to that obtained on working out the reaction mixture as usual. It seems that the cyclisation process occurs spontaneously after the formation of (**3**). This novel reaction represents an easy convenient one-step method for the synthesis of 4-arylphthalaz-1-ones from the readily-available N-aminophthalimide.

This investigation was extended to involve another one-step method for the synthesis of 4-alkyl- or 4-arylphthalaz-1-ones that allows the introduction of different substituents in the 4-position of phthalazinone ring that are difficult to introduce by the previous method or other known methods.[1-4] This method involves the reaction of N-aminophthalimide with Grignard reagents. Thus, when N-aminophthalimide is allowed to react with o-methoxyphenyl-, m-tolyl- or α-naphthylmagnesium bromides, the corresponding 4-arylphthalaz-1-ones (**2f–h**) are obtained in moderate yields. This reaction seems also to involve the intermediate formation of the o-aroylbenzoic acid hydrazides (**3**). Benzylmagnesium chloride reacts similarly with (**1**) to give 4-benzylphthalaz-1-one (**4**).



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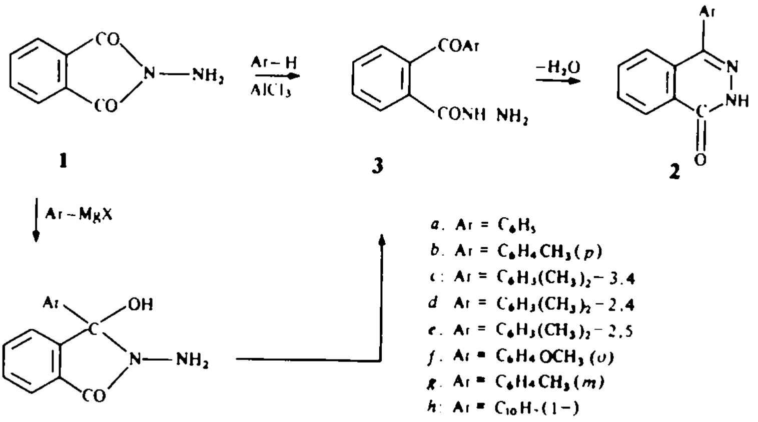
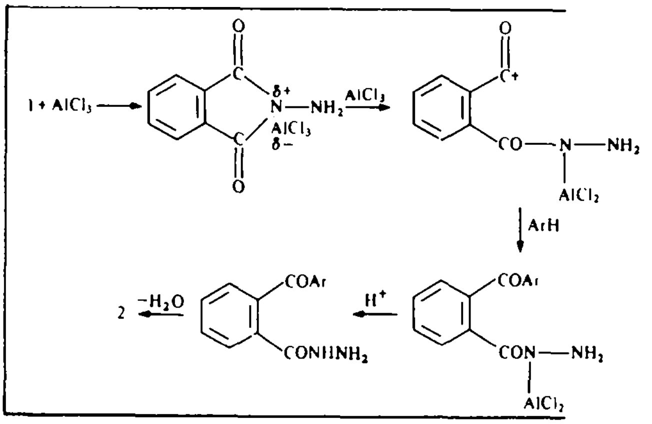
The structure assigned to the products of the above reactions is confirmed by: (i) Microanalytical data. (ii) Their infrared spectra are similar to those pre-



a. Ar = C_6H_5
b. Ar = $C_6H_4CH_3$(*p*)
c: Ar = $C_6H_3(CH_3)_2$−3.4
d Ar = $C_6H_3(CH_3)_2$−2.4
e. Ar = $C_6H_3(CH_3)_2$−2.5
f. Ar = $C_6H_4OCH_3$ (*o*)
g. Ar = $C_6H_4CH_3$(*m*)
h: Ar = $C_{10}H_7$(1−)

viously reported for 4-arylphthalaz-1-ones.[3,4] They show strong absorption at 1660–1675 cm^{-1}, characteristic of carbonyl stretching frequencies of cyclic amides in addition to broad bands at 2895–3185 cm^{-1} characteristic of NH and OH stretching frequencies indicating the presence of the HN-CO $\rightleftharpoons$ N=C–OH grouping (*cf.* Experimental section). (iii) The structure was rigidly established by the identity (m.p., mixed m.p., and superimposable IR spectra) of **2a**, **b** and **4** with authentic samples prepared by the reaction of hydrazine hydrate with o-benzoyl-,[1] o, p. toluoyl[2]-benzoic acids, and 3-benzalphthalide,[3] respectively.

A possible mechanism for the Friedel–Crafts reaction of N-aminophthalimide with aromatic hydrocarbons can be outlined as follows



EXPERIMENTAL

All m.ps are uncorrected, Microanalytical data were carried out in Microanalytical Laboratories, El-Nasr Company for Pharmaceutical Chemicals and Cairo University. Infrared spectra were measured on a Pye Unicam 1200 using the KBr disc technique.

Reaction of N-aminophthalimide with aromatic hydrocarbons under Friedel-Crafts conditions: formation of 4-arylphthalaz-1-ones (**2**)

General procedure. Anhydrous aluminium chloride (3.34 g, 0.025 mole) was added portionwise to a stirred cold (ice-bath) soln of N-aminophthalimide (0.01 mole) in the aromatic hydrocarbon (50 ml). The reaction mixture was stirred for 1 hr at room temp., then the stirring was continued for further 4 hr on a boiling water bath. The reaction mixture was left overnight at room temp. and then hydrolysed by the addition of ice and conc. HCl. The resulting mixture was steam distilled to remove the excess solvent. The residual organic solid product was filtered off and crystallised from benzene to give the corresponding 4-arylphthalaz-1-ones.

4-Phenylphthalaz-1-one (**2a**), m.p. 232–4°, yield 77%, calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61; Found: C, 75.60; H, 4.30; N, 12.60%; IR ($\nu_{NH.OH}$2900–3180 cm^{-1}, $\nu_{C=O}$1670 cm^{-1}). The product showed no depression on admixture with an authentic specimen prepared by the action of hydrazine hydrate on o-benzoyl-benzoic acid.[1]

4-p-Tolylphthalaz-1-one (**2b**), m.p. 259–260°, yield 74%, calc for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.08; N, 11.86; Found: C, 76.20; H, 4.90; N, 12.0%. IR ($\nu_{NH.OH}$2900–3160 cm^{-1}, $\nu_{C=O}$1668 cm^{-1}). The product showed no depression on admixture with authentic specimen prepared by the action of hydrazine hydrate on p-toluoylbenzoic acid.[2]

4-(3',4'-dimethylphenyl)phthalaz-1-one (**2c**), m.p. 236–237°, yield 71%, calc for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.6; N, 11.2; Found: C, 77.0; H, 5.8; N, 11.1%. IR ($\nu_{NH.OH}$2920–3175 cm^{-1}, $\nu_{C=O}$1675 cm^{-1}).

4-(2',4'-dimethylphenyl)phthalaz-1-one (**2d**), m.p. 243–244°, yield 72%, calc for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.6; N, 11.2; Found: C, 76.8; H, 5.6; N, 10.8%. IR ($\nu_{NH.OH}$2900–3180 cm^{-1}, $\nu_{C=O}$1665 cm^{-1}).

4-(2',5'-Dimethylphenyl)phthalaz-1-one (**2e**), m.p. 256–257°, yield 78%, calc for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.6; N, 11.2; Found: C, 77.2; H, 5.2; N, 11.5%. IR ($\nu_{NH.OH}$2895–3160 cm^{-1}, $\nu_{C=O}$1660 cm^{-1}).

Action of Grignard reagents on N-aminophthalimide: formation of 4-alkyl- or 4-arylphthalaz-1-ones

General procedure. A soln of the appropriate Grignard reagent (0.03 mole) in dry ether (50 ml) was added to a soln of N-aminophthalimide (0.01 mole) in dry benzene (60 ml) with occasional shaking. The reaction mixture was heated under reflux on a boiling water bath for 5 hr and left overnight. The reaction mixture was then hyrolysed by shaking with sat. aq. NH_4Cl. The benzene–ether layer was washed several times with cold water, separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The reaction product formed after cooling was crystallised from the suitable solvent to give the corresponding phthalaz-1-ones as colourless crystals.

4-Benzylphthalaz-1-one (**4**). Crystallised from benzene–light petroleum (b.p. 60–80°), m.p. 201°, yield 52%, calc for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.08; N, 11.86; Found: C, 76.50; H, 5.20; N, 11.5%. IR ($\nu_{NH.OH}$2910–3180 cm^{-1}, $\nu_{C=O}$1660 cm^{-1}). The product showed no depression when admixed with an authentic sample prepared by the action of hydrazine hydrate on 3-benzalphthalide.[3]

4-o-Methoxyphenylphthalaz-1-one (**2f**). Crystallised from benzene, m.p. 248–249°, yield 63%, calc for $C_{15}H_{12}N_2O_2$: C, 71.43; H, 4.76; N, 11.11; Found: C, 71.10; H, 4.80; N, 11.10%. IR ($\nu_{NH.OH}$2900–3180 cm^{-1}, $\nu_{C=O}$1660 cm^{-1}).

4-m-Tolylphthalaz-1-one (**2g**). Crystallised from benzene-light petroleum (b.p. 100–120°), m.p. 202–203°, yield 70%, calc for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.08; N, 11.86; Found: C, 76.5; H, 5.3; N, 11.2%. IR ($\nu_{NH.OH}$2900–3170 cm^{-1}, $\nu_{C=O}$1660 cm^{-1}).

4-α-Naphthylphthalaz-1-one (**2h**). Crystallised from glacial acetic acid, m.p. 226–227°, yield 65%, calc for $C_{18}H_{12}N_2O$: C, 79.4; H, 4.4; N, 10.3; Found: C, 80.1; H, 4.5; N, 10.3%. IR ($\nu_{NH.OH}$2910–3185 cm^{-1}, $\nu_{C=O}$1660 cm^{-1}).

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