

Promotion of the Catalytic Hydrogenation of Phthalimide and Substituted Phthalimides over Palladium

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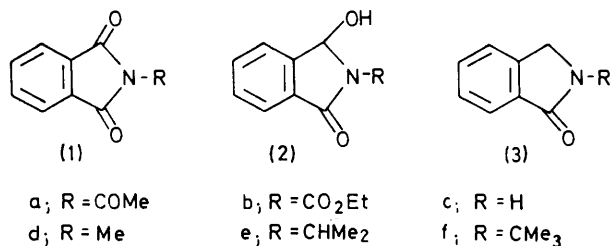
Phthalimide undergoes quantitative conversion into isoindolin-1-one (3c) upon hydrogenation in ethyl acetate over 10% palladium-carbon in the presence of trifluoroacetic acid, but resists reduction in its absence. This reaction is also promoted by iron(II) sulphate. The effect of *N*- and ring-substitution on the trifluoroacetic acid-promoted reduction has been investigated.

WE have shown¹ that the presence of certain electron-withdrawing substituents on the imide nitrogen atom allows the hydrogenation of phthalimides (1) to the corresponding 3-hydroxyisoindolin-1-ones (2) over 10% palladium-charcoal in ethyl acetate; phthalimide and *N*-methylphthalimide survive these conditions. If this hydrogenation of imides involves¹ a nucleophilic attack

on a carbonyl carbon atom then one might expect that the reaction would be promoted by acid. We have found this to be the case. Thus, in the presence of trifluoroacetic acid, reductions of *N*-acetyl- and *N*-methoxycarbonyl-phthalimides (1a and b) are markedly

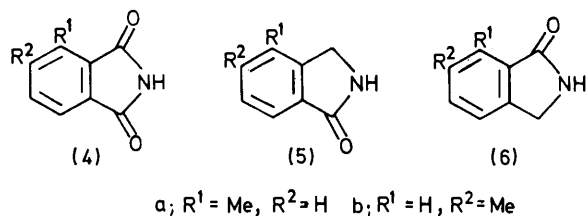
¹ A. J. McAlees and R. McCrindle, *J. Chem. Soc. (C)*, 1969, 2425.

accelerated, and phthalimide (1c) and *N*-alkylphthalimides (1d–f) now react. Under these conditions the sole products are isoindolin-1-ones (3), which presumably arise by hydrogenolysis of intermediate 3-hydroxy-derivatives (2). The relative rates observed



for these reactions [(1a) > (1b) > (1c) > (1d) > (1e) ~ (1f)] are in the order to be expected if nucleophilic attack on a carbonyl carbon atom were involved. As expected,¹ even in the presence of trifluoroacetic acid, hexahydrophthalimide and *N*-ethoxycarbonylsuccinimide resisted hydrogenation.

The effect of substitution on the aromatic ring was investigated by using 3- and 4-methylphthalimides (4a and b). Both underwent reduction more slowly than phthalimide itself, the rate for the 3-isomer (4a) being significantly less than that for the 4-isomer (4b), in



accord with the mechanism mentioned above. In contrast to our previous observations² on 3- and 4-methylphthalic anhydrides, reduction occurs preferentially at the carbonyl group *meta* to the methyl substituent in both phthalimides. In the case of the anhydrides we proposed² that nucleophilic attack on the carbon of the carbonyl group is facilitated by protonation of this group. It appears that for the imides, either both carbonyl groups are protonated or if only one is protonated then productive nucleophilic takes place at the other. Attack on the protonated carbonyl group would require departure of an amide anion on ring opening; the equivalent reaction for an anhydride would produce a carboxylate anion.

Numerous reports³ indicate that the hydrogenation of carbonyl functions may be promoted by the addition of small amounts of certain metal salts, particularly those of iron. We have found that phthalimide (1c) can be reduced to isoindolin-1-one (3c) over 10% palladium-carbon in ethyl acetate if a small amount of iron(II) sulphate is added.

² A. J. McAlees, R. McCrindle, and D. W. Sneddon, *J.C.S. Perkin I*, 1977, 2030.

EXPERIMENTAL

General details have been outlined previously.²

Hydrogenations.—Unless specified otherwise a solution of the imide (1.0 g) and trifluoroacetic acid (5.0 ml) was stirred in ethyl acetate (100 ml) with 10% palladium-carbon (1.0 g) under hydrogen.

Phthalimide (1c). (a) The imide absorbed 2 mol. equiv. of hydrogen within 8 h. T.l.c. of the residue after work-up showed the presence of one product. Trituration with light petroleum gave isoindolin-1-one (3c) (0.85 g), needles, m.p. 150–151° (lit.,⁴ 150°).

(b) Use of less catalyst (0.1 g) gave (3c) (0.85 g), with uptake of 2 mol. equiv. of hydrogen during 35 h.

(c) With the reduced catalyst load (0.1 g) but increased concentration (20% by volume) of trifluoroacetic acid, the reduction was complete within 12 h and gave (3c) (0.80 g).

(d) Phthalimide, when stirred in ethyl acetate (100 ml) with iron(II) sulphate (50 mg) and 10% palladium-carbon (1.0 g), absorbed 2 mol. equiv. of hydrogen during 34 h to give (3c) (0.80 g).

***N*-Methylphthalimide (1d).** This imide consumed 2 mol. equiv. of hydrogen within 12 h. T.l.c. showed the presence of one product, *N*-methylisoindolin-1-one (3d) (0.95 g), which on work-up crystallised from light petroleum, m.p. 115–117° (lit.,⁵ 118–120°).

***N*-Isopropylphthalimide (1e).** The imide absorbed *ca.* 1.5 mol. equiv. of hydrogen during 32 h, after which hydrogenation was stopped. T.l.c. showed the presence of substrate and a product identified by n.m.r. analysis as *N*-isopropylisoindolin-1-one (3e) [(1e) : (3e) 2 : 3]; $\tau(\text{CCl}_4)$ 2.35br (s, aromatic) (1e), 2.59br (s, aromatic) (3e), 5.2–5.9 (m, NCH) [(1e) + (3e)], 5.68 (s, NCH₂) (3e), 8.57 (d, *J* 7 Hz, H_{CMe₂}) (1e), and 8.76 (d, *J* 7 Hz, CHMe₂) (3e).

***N*-*t*-Butylphthalimide (1f).** This imide absorbed *ca.* 1.7 mol. equiv. of hydrogen during 43 h. T.l.c. showed the presence of substrate and a more polar component, identified as *N*-*t*-butylisoindolin-1-one (3f) by n.m.r. analysis [(1f) : (3f) 3 : 7]; $\tau(\text{CDCl}_3)$ 2.35br (s, aromatic) (1f), 2.57br (s, aromatic) (3f), 5.55 (s, NCH₂) (3f), 8.34 (s, Bu^t) (1f), and 8.48 (s, Bu^t) (3f).

***N*-Acetylphthalimide (1a).** Two mol. equiv. of hydrogen were absorbed by this substrate during 2 h. The single product, *N*-acetylisoindolin-1-one (3a) (0.78 g), crystallised from light petroleum; m.p. 152–153° (lit.,⁴ 151°).

***N*-Ethoxycarbonylphthalimide (1b).** This imide absorbed 2 mol. equiv. of hydrogen during 3 h. The sole product, *N*-ethoxycarbonylisoindolin-1-one (3b) (0.85 g), crystallised from ethyl acetate-light petroleum; m.p. 130°; ν_{max} 1710 and 1730 cm⁻¹; $\tau(\text{CDCl}_3)$ 2.1–2.8 (m, aromatic), 5.25 (s, NCH₂), 5.64 (q, CH₂·CH₃), *J* 7 Hz), and 8.62 (t, CH₂·CH₃, *J* 7 Hz) (Found: C, 64.35; H, 5.55; N, 6.8. C₁₁H₁₁NO₃ requires C, 64.4; H, 5.4; N, 6.85%).

3-Methylphthalimide (4a). This substrate consumed 2 mol. equiv. of hydrogen within 30 h. Work-up gave a solid (0.92 g) mixture (n.m.r.) of 4-methylisoindolin-1-one (5a) (26%) and 7-methylisoindolin-1-one (6a) (74%); $\tau(\text{CDCl}_3)$ 2.2–2.9 (m, aromatic), 5.51br (s, NCH₂), 7.35 (s, CH₃) (6a), and 7.61 (s, CH₃) (5a).

4-Methylphthalimide (4b).—The imide absorbed 2 mol.

³ R. Baltzly, *J. Org. Chem.*, 1976, **41**, 933 and references cited therein.

⁴ C. Graebe, *Annalen*, 1888, **247**, 288.

⁵ O. Fischer and H. Wolter, *J. prakt. Chem.*, 1909, **80**, 102.

equiv. of hydrogen over 16 h. Work-up gave a white crystalline solid (0.96 g) mixture (n.m.r.) of 5-methylisindolin-1-one (5b) (64%) and 6-methylisindolin-1-one (6b) (36%); τ (220 MHz; CDCl_3) 1.26br (s, NH), 2.27 (d, H-7, J 8 Hz) (5b), 2.36 (s, H-7) (6b), 2.57br (d, H-5, J 8 Hz) (6b), 2.60 (d, H-4, J 8 Hz) (6b), 2.68 (s, H-4) (5b), 2.70 (d, H-6, J 8 Hz) (5b), 5.50br (s, NCH_2), and 7.52 and 7.55 (both s, CH_3).

Hexahydrophthalimide. Little or no hydrogen was

absorbed during 26 h by this imide and only substrate (0.95 g) was recovered.

N-Ethoxycarbonylsuccinimide. This imide was recovered quantitatively from attempted hydrogenation under the conditions outlined above.

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