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An expedient synthesis of homophthalimides

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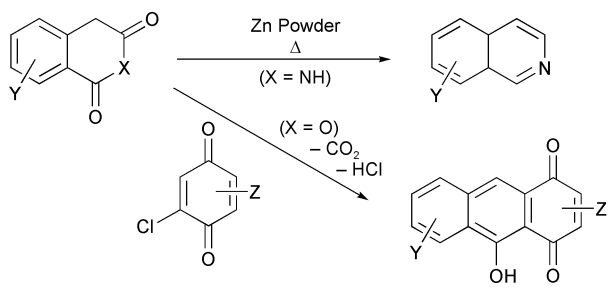
The six-membered heterocyclic subunit of homophthalimides can be obtained by a direct, hitherto unprecedented, radical cyclisation onto an aromatic ring starting from a xanthate precursor.

Homophthalic acid derivatives are important building blocks for the synthesis of alkaloids, dyes, and a variety of medicinally interesting structures.[1] They are also convenient precursors of *o*-quinonemethide intermediates, which readily undergo Diels–Alder cycloadditions vith various reactive dienophiles (*e.g.* quinones for the synthesis of anthracyclinones as in Scheme 1)[2] or of isoquinolines through vigourous heating with zinc powder, a reaction also pictured in Scheme 1 and first described by Le Blanc in the 19th century.[3]

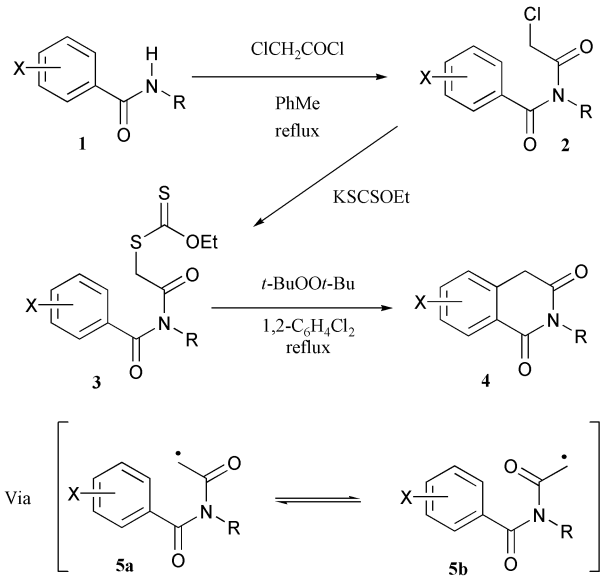
Synthetic routes to these deceptively simple compounds are, surprisingly, scarce and of very limited scope.[1,4] Copper catalysed aromatic substitution of 2-halobenzoic acids and the oxidative ring cleavage of indanones are the two main routes to homophthalic acids, and therefrom to homophthalimides. Except in the simplest of cases, the substrates needed in both of these approaches are not generally available. In the present communication, we describe a practical synthesis based on a radical cyclisation onto an aromatic ring which leads directly to homophthalimides.

Our approach is delineated in Scheme 2 and relies on a versatile radical chemistry of xanthates we have developed over the past few years.[5] The key aspect is the degeneracy of the reaction of radical **5** with its xanthate precursor **3**. This reactive intermediate is therefore not irreversibly consumed and acquires a comparatively long lifetime, allowing it to overcome both the rotational barrier of the amide linkage (equilibrium between **5a** and **5b**) and the quite slow ring-closure onto the aromatic ring. This step is then followed by an oxidative rearomatisation, involving the peroxide or resulting from a disproportionation process.[6] In any case, stoichiometric amounts of peroxide are required.

After some experimentation, we found that heating xanthates **3** in refluxing *o*-dichlorobenzene with addition of 1.0 molar equivalent of di-*tert*-butyl peroxide brought about the desired transformation in acceptable yield, as shown by the examples collected in Fig. 1. The products very often precipitated upon cooling of the reaction mixture or after evaporation of part of the solvent under reduced pressure, and could be isolated by *mere filtration*.† The use of a high boiling solvent shortens the reaction time by allowing a convenient decomposition rate of the peroxide[7] and increases the rate of interchange between the two rotational isomers of the intermediate radical.[8] The xanthate precursors are readily accessible by reaction of the



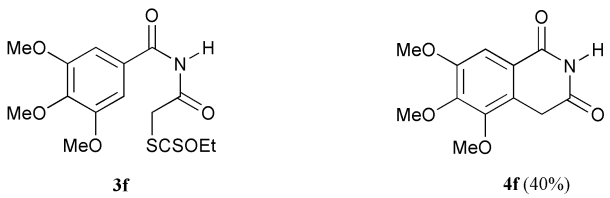
Scheme 1 Synthesis of isoquinolines from homophthalimides.



Scheme 2 Synthesis of homophthalimides.

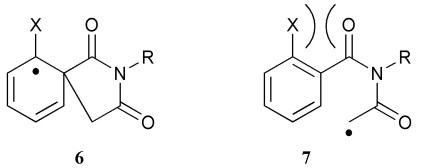
3a, X = F ; R = H
3b, X = Cl ; R = H
3c, X = Br ; R = H
3d, X = I ; R = H
3e, X = CF_3 ; R = H
3g, X = H ; R = Me

4a, X = F ; R = H (56%)
4b, X = Cl ; R = H (52%)
4c, X = Br ; R = H (60%)
4d, X = I ; R = H (65%)
4e, X = CF_3 ; R = H (40%)
4g, X = H ; R = Me (56%)



3f

4f (40%)



6 **7**

Fig. 1

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corresponding benzamides **1** with chloroacetyl chloride, followed by displacement of the chlorine in chloracetimide **2** with commercially available potassium *O*-ethyl xanthate.

Interestingly, homophthalimides both substituted and unsubstituted at the nitrogen may be obtained. Radical ring closure of unsubstituted amides is very rare (for an example, see ref. 9*a*; it is usually necessary to place a substituent—preferably bulky—on the nitrogen atom[9*b*]) and, as far as we know, unprecedented for the formation of six-membered rings fused to an aromatic ring. Such cyclisations would be exeedingly difficult to perform by more traditional radical methods, especially those based on stannane chemistry, since premature capture of intermediate radical **5** would be almost impossible to avoid. The success of the present procedure hinges to a large extent on the long lifetime of intermediate radical **5** when generated using the xanthate technology; moreover, as illustrated by examples **4c** and **4d**, the method tolerates the presence of bromine and iodine on the aromatic ring, allowing for further modifications using various powerful transition metal coupling reactions.

The reaction works best with substrates where the substituents are symmetrically arranged around the aromatic ring, to avoid the formation of regioisomers (as for example with *meta*-substituted precursors). In the case of *ortho*-substituted derivatives we encountered a serious complication from *ipso*-substitution (*cf.* **6**) and complex mixtures were observed. This is presumably due to a peri-type steric repulsion, shown in **7**, which hampers the adoption by the intermediate radical of a conformation propitious for the desired cyclisation.

In summary, this approach provides a flexible and rapid route to otherwise inaccessible homophthalimides and, therefrom, to homophthalic acids and anhydrides. It allies simplicity with the use of readily available, cheap substrates and reagents. The isolation of the crude product by a simple filtration directly from the reaction mixture is a distinct asset for large scale preparations.†

Notes and references

† *Typical experimental procedure*: synthesis of xanthates **3a**–**f**: The corresponding benzamide **1** (1 mmol) was refluxed in toluene (2 ml) in the presence of chloroacetyl chloride (1.5 mmol) until complete reaction (TLC monitoring). The reaction mixture was cooled and the precipitated chloroacetimide **2** filtered, dried, and used directly in the next step. The chloroacetimide was treated under argon with potassium *O*-ethyl xanthate (1.1 mmol) in acetonitrile (2–2.5 ml). Addition of water gave a precipitate which was filtered off, washed with water and dried. The xanthate **3** thus obtained (overall yield 80-95%) was used directly in the next step.

Synthesis of homophthalimides **4**: a solution of the xanthate **3a**–**g** (1 mmol) in *o*-dichlorobenzene (4 ml) was refuxed under argon for 15 min. Then a solution of di-*tert*-butyl peroxide (1 mmol.) in *o*-dichlorobenzene (3 ml) was added over a periode of 60–90 min. After cooling the mixture, the precipitate was filtered off and dried. Analytical samples were obtained by sublimation. Chromatography on silica gel were necessary for compounds **4a** and **4e**.

Spectral and analytical data for new homophthalimides **4a**–**f** (**4g** has been described in ref. 1*d*): **4a**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.4 (br s, 1H, NH), 8.1 (dd, 1H, *J* 6 Hz, Ph), 7.3 (m, 2H, Ph), 4.1 (CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.6, 164.4 (CO), 166.9, 162.9 (CF, J_{CF} 252 Hz), 140.0, 139.8, 130.6, 130.4 (J_{CF} 10 Hz), 121.8 (*C*Ph), 114.9, 114.6, 114.4, 114.1 (*J* 22 Hz, *C*HPh), 35.7 (CH_2). IR (Nujol, ν_{max}) 1705, 1689 (CO). Mp 244 °C. Anal. Calc. for $C_9H_6FNO_2$: C 60.34, H 3.38, found: C 60.31, H 3.37%. **4b**: ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.5 (br s, 1H, NH), 8.0 (d, 1H, *J* 8.9 Hz, Ph), 7.5 (s + d, 2H, Ph), 4.1 (CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 170.4, 164.5 (CO), 138.8, 138.2 (C*Ph*), 129.3, 127.5, 127.4 (*C*HPh), 123.9 (*C*Ph), 35.7 (CH_2). IR (Nujol, ν_{max}) 1702, 1689 (CO). Mp 267–268 °C (decomp.). Anal. Calc. for $C_9H_6ClNO_2$: C 55.26, H 3.09, found: C 55.21, H 3.28%. **4c**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.5 (br s, 1H, NH), 8.03 (d, 1H, *J* 8.9 Hz, Ph), 7.7 (s + d, 2H, Ph), 4.15 (CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6) 170.4, 164.6 (CO), 138.9 (*C*Ph), 130.5, 130.3, 129.3 (*C*HPh), 127.3, 124.2 (*C*Ph), 35.7 (CH_2). IR (Nujol, ν_{max}) 1702, 1695 (CO). Mp 278–280 °C (decomp.). Anal. Calc. for $C_9H_6BrNO_2$: C 45.03, H 2.52, found: C 45.32, H 2.53%. **4d**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.5 (br s, 1H, NH), 7.93 (s + d, 2H, Ph), 7.83 (d, 1H, *J* 8.6 Hz, Ph), 4.1 (CH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 170.4, 164.9 (CO), 138.5 (C*Ph*), 136.4, 136.0, 128.9 (*C*HPh), 124.4 (*C*Ph), 101.9 (CI), 35.4 (CH_2). IR (Nujol, ν_{max}) 1703, 1698 (CO). Mp 266–267 °C. Anal. Calc. for $C_9H_6INO_2$: C 37.66, H 2.11, found: C 37.51, H 2.21%. **4e**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.6 (br s, 1H, NH), 8.32 (d, 1H, *J* 9 Hz, Ph), 7.92 (s + d, 2H, Ph), 4.2 (CH_2). IR (Nujol, ν_{max}) 1703, 1698 (CO). Mp 238–239 °C (decomp.). Anal. Calc. for $C_{10}H_6F_3NO_2$: C 52.41, H 2.64, found: C 52.69, H 2.61%. **4f**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.37 (s, 1H, NH), 7.47 (s, 1H, Ph), 3.97, 3.96, 3.94 (3s, 9H, OCH_3). 3.89 (s, 2H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) 170.7, 164.6 (CO), 152.4, 149.3, 146.1, 123.3, 120.0 (*C*Ph), 105.6 (*C*HPh), 60.5, 60.4, 55.9 (3 OMe), 31.3 (CH_2). MS (IC, NH_3, *m*/*z*) 252 $(MH)^+$, 269 $(MH + NH_3)^+$. IR (ν_{max}, Nujol) 1705, 1686 (CO). Mp 206–207 °C (decomp.). Anal. Calc. for $C_{12}H_{13}NO_5$: C 57.37, H 5.22, found: C 57.16, H 5.27%.

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