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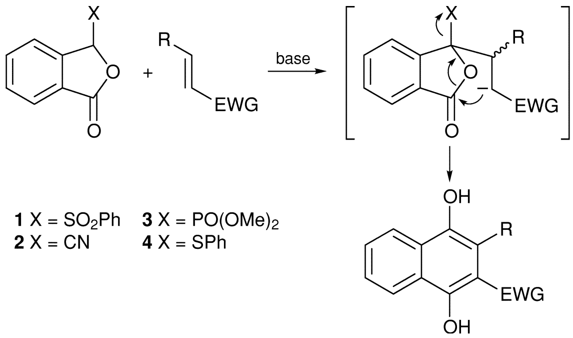
3-(Phenylthio)phthalide: an Expedient Reagent in Phthalide Annulation†

Sujit K. Ghorai, Harendra N. Roy, Mousumi Bandopadhyay and Dipakranjan Mal*

Department of Chemistry, Indian Institute of Technology, Kharagpur, 721 302, India

3-(Phenylthio)phthalide **4** is more readily accessible than the established reagents **1** and **2** and can be engaged in phthalide annulation with comparable efficacy.

The annulation[1] of 3-(phenylsulfonyl)phthalide **1**[2] or 3-cyanophthalide **2**[3] with Michael acceptors, depicted in eqn. (1) is one of the most attractive routes to 1,4-dioxygenated linear fused aromatics or hydroaromatics. Since their introduction in 1978 independently by Hauser *et al.* and Kraus *et al.*, these two classes of reagents and their substituted derivatives have been widely utilised in the total synthesis of many naturally occurring complex polyketides.[1] The process involves Michael addition of the carbanion of **1** or **2** to an electron-deficient olefin followed by base-induced cyclisation accompanied by expulsion of the 3-substituent to furnish the annulated product [eqn. (1)].



(1)

The efficiency of the annulation to a large extent depends on the nature of the substituent at C-3 of the reagents, but the base, solvent, temperature and electron withdrawing groups in Michael acceptors also have an effect. For example, dimethyl phthalide-3-phosphonate **3**, recently introduced by Watanabe *et al.*, seems to work better than sulfonylphthalide **1** or cyanophthalide **2**.[4] Of the Hauser synthon **1** and the Kraus synthon **2**, the latter has gained more popularity because of its cleaner reaction[5] though the former is more conveniently prepared from phthalaldehydic acid.[6] The use of 3-(phenylthio)phthalide **4** as an annulating agent was contemplated about two decades ago. But the initial experiments with **4** resulted in only Michael addition products.[7] Thereafter, it received very scant attention despite the fact that under optimized conditions ($\mathrm{Bu^tOK}$, DMSO, room temp.) it can be annulated with a small number of conjugated enones in modest yields.[8] In the course of our studies with thiophthalides, we noted that 3-(phenylthio)-thiophthalides are much better annulating agents than their phenylsulfonyl analogs.[9] The superiority of the former was ascribed to the smaller steric bulk of the –SPh group than that of –SO$_2$Ph. More recently, a similar trend has been observed by Tso *et al.* with 3-(phenylthio)phthalide **4** in annulation with vinyl sulfones *en route* to vitamin K.[2] These findings prompted us to reexamine the reactivity of **4** in phthalide annulation with various Michael acceptors. We now report that in the presence of lithium *tert*-butoxide, 3-(phenylthio)phthalide **4** undergoes facile annulation with α,β-unsaturated enones, esters, nitriles and quinone monoketals, in excellent yields. It should also be noted that compound **4**[7] is more readily accessible than **1**–**3**.

In a typical run, phthalide **4** is treated with a solution of $\mathrm{Bu^tOLi}$ in THF under an argon atmosphere at –60 °C for 15–20 min and then with a Michael acceptor (1.1–1.5 equiv.) for 1 h at –60 °C. The reaction mixture is further stirred under ambient conditions for a few hours. Acidic work-up followed by evaporation of the solvents often affords a solid, which is either recrystallized or chromatographed to yield the annulated product. The results are summarized in Table 1. For the non-enolizable enones (entries 2–4) or lactone (entry 1), 1.1–1.2 equiv. of Michael acceptor is sufficient for excellent results. On the other hand, a slight excess of Michael acceptor is required for polymerizable or enolizable acceptors (entries 7–9). Entry 4 is noteworthy, since the corresponding Michael acceptor fails to undergo annulation with phthalide sulfone **1**, once again implying the importance of the steric bulk of the –SPh group in comparison with the –SO$_2$Ph group. Both (phenylthio)phthalide **4** and cyanophthalide **2**, however, react with the enone (entry 4) with equal effectiveness. The key to the success is the choice of the base, *i.e.* $\mathrm{Bu^tOLi}$,[15] which over the years has proved to be superior to bases such as lithium diisopropylamide, dimsylsodium, $\mathrm{Bu^tOK}$, NaH or lithium hexamethyldisilazide in such annulations.[4] In summary, the use of 3-(phenylthio)phthalide **4** in place of **1** and **2** results in a practical improvement in the phthalide annulation protocol.

Experimental

^{1}H NMR spectra were recorded on a Bruker AC200 MHz instrument for solutions in $CDCl_3$ unless otherwise mentioned and *J* values are given in Hz. Melting points are uncorrected. The reagent **4**[7] and the Michael acceptors used for entries 2,[11] 3,[12] 4,[11] 5[13] and 7[14] were prepared according to the respective literature procedure.

General Annulation Procedure.—To a stirred solution of lithium *tert*-butoxide (3.0 mmol) in THF (20 ml) at –60 °C ($CHCl_3$–liquid N_2 bath) under argon atmosphere was added 3-(phenylthio)-phthalide **4** (1.0 mmol), and stirring was continued for 15–20 min, after which Michael acceptor (1.1–3.0 equiv. as specified in Table 1) as a solution in THF (5 ml) was introduced. The resulting mixture was stirred at –60 °C for about 30 min and then allowed to reach ambient temperature and stirred for another 3–16 h till the reaction showed no further change on TLC. The reaction mixture was quenched with 20% HCl solution and concentrated under reduced pressure. Generally, a solid appeared at this point, which was filtered, dried and recrystallized. If the solid did not appear, the mixture was extracted with ethyl acetate (3 × 30 ml). The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The concentrated mass was crystallized from diethyl ether–light petroleum or chromatographed (silica gel) if necessary.

Selected Physical Data.—Compound **5**: mp 253 °C (lit.,[10] mp 253–254 °C); ν_{max}/cm^{-1} (KBr) 1650; δ_H ($CDCl_3$–[$^2H_6$] DMSO) 12.62 (s, 1 H), 9.30 (d, 1 H, *J* 6.2), 8.86 (s, 1 H), 8.42 (d, 1 H, *J* 8.2), 8.31

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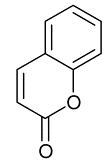
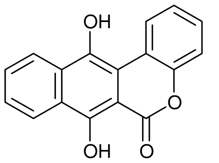
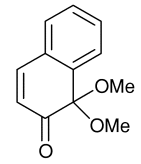
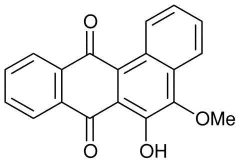
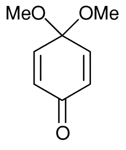
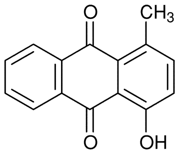
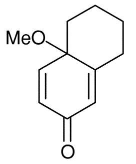
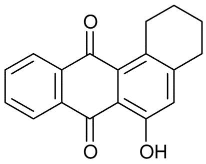
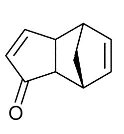
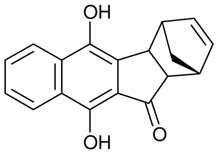
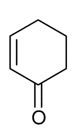
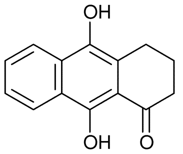
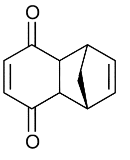
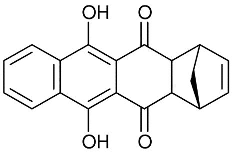
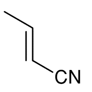
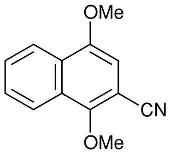
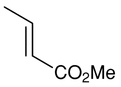
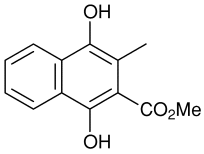
*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Annulation of 3-(phenylthio)phthalide **4** with Michael acceptors

Entry	Michael acceptor	(equiv.)	Product		Yield (%)[a]
1		(1.1)		**5**	94
2		(1.1)		**6**	92
3		(1.1)		**7**	95
4		(1.2)		**8**	87
5		(1.2)		**9**	95
6		(1.5)		**10**	90
7		(2.0)		**11**	58
8		(3.0)		**12**	76[b]
9		(1.5)		**13**	61

[a]Isolated yields. [b]The crude product was methylated with Me_2SO_4–K_2CO_3.

(d, 1 H, *J* 8.4), 7.68 (t, 1 H, *J* 7.4), 7.53 (t, 1 H, *J* 8.0), 7.22–7.34 (m, 3 H).

Compound **9**: mp 228–229 °C; ν_{max}/cm^{-1} (KBr) 1631; δ_H ($CDCl_3$–[$^2H_6$] DMSO) 9.72 (br s, 1 H), 8.19 (d, 1 H, *J* 8.8), 8.15 (d, 1 H, *J* 8.8), 7.79 (br s.1 H), 7.54 (dt, 1 H, *J* 1.4, 7.2), 7.4 (dt, 1 H, *J* 1.0, 7.2), 5.87 (dd, 1 H, *J* 2.8, 5.6). 5.54 (dd, 1 H, *J* 2.8, 5.6), 4.00 (dd, 1 H, *J* 4, 6.8), 3.50 (br s, 1 H), 3.32 (br s, 1 H), 3.26 (dd, 1 H, *J* 4.6, 6.8), 1.80–1.60 (m, 2 H). MS (*m*/*z*): 278, 259, 248, 231, 212, 183, 155, 128, 66.

Compound **11**: mp 143–144 °C (yellow); ν_{max}/cm^{-1} (KBr) 3421, 1719, 1609; δ_H 14.47 (s, 2 H), 8.43 (dd, 2 H, *J* 3.2, 6.2), 7.75 (dd, 2 H, *J* 3.2, 6.2), 6.05 (s, 2 H), 3.71 (s, 2 H), 3.45 (s, 2 H); 1.56 (br s, 2 H); *m*/*z* (306), 293 (100%).

Compound **13**: mp 139 °C; ν_{max}/cm^{-1} (KBr) 3442, 1622; δ_H 12.03 (s, 1 H, D_2O exchangeable), 8.37 (dd, 1 H, *J* 1.2, 8.2), 8.01 (d, 1 H, *J* 8.4), 7.61 (dt, 1 H, *J* 1.2, 7.8), 7.47 (dt, 1 H, *J* 1.2, 8.2), 4.62 (s, 1 H, D_2O exchangeable), 4.01 (s, 3 H), 2.54 (s, 3 H); δ_C 172.5, 156.4, 1456.1, 141.0, 129.2, 128.4, 125.4, 124.0, 120.8, 115.2, 106.1, 52.0, 14.6 (Calc. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17; Found C, 67.19; H, 5.06%).

Compounds **5**,[10] **6**,[11] **7**,[12] **8**,[11] **10**,[4] **12**[16] were characterized by comparison of their physical data with those described in the literature. Compounds **9** and **11** were characterized by transforming them into their known dimethyl ethers.[9,13]

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