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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2635–2638

4-Fluorocyclohexa-2,5-dienones as new acceptors for the Hauser annulation

Pallab Pahari, Bidyut Senapati and Dipakranjan Mal*

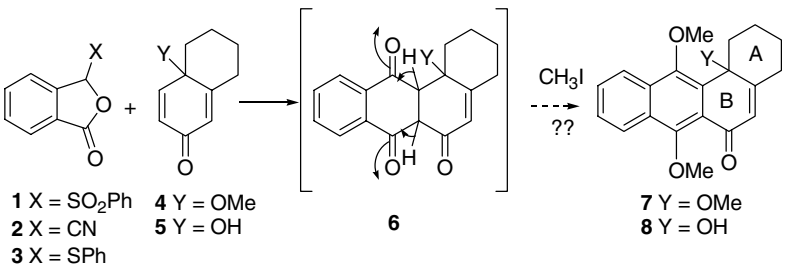
Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

Received 21 November 2006; revised 24 January 2007; accepted 31 January 2007
Available online 3 February 2007

Abstract—4-Fluorocyclohexa-2,5-dienones are introduced as new acceptors for the Hauser annulation. In cases where the corresponding methoxy analogs fail to undergo annulation, the former smoothly do so with phenylsulfonylphthalides to furnish anthraquinones in good yields. Steric effects are implicated to explain the inertness of the methoxy analogs.

The common occurrence of quinone nuclei in natural products has provided considerable impetus for synthetic endeavors.[1] In the past decade, this has been accelerated by the discovery of a variety of newer quinonoid molecules exhibiting antifilarial,[2] antitumour,[3] antimalarial[4] and antidiabetic activities.[5] Whilst numerous synthetic strategies exist in the literature for the synthesis of quinonoids, few have proved to be more general than the Hauser annulation.[6] Among donors, the most widely used are 3-phenylsulfonylphthalides (e.g., **1**) and 3-cyanophthalides (e.g., **2**).[7] Recently, phenylsulfanylphthalides (e.g., **3**) have been utilized with remarkable success.[8] Due to the hazards associated with the preparation of cyanophthalides using KCN, phthalide sulfones are preferred as the Hauser donors. However, there are instances where annulations with phenylsulfonylphthalides **1** (Scheme 1) fail. These results were interpreted in terms of both electronic and steric effects. Nevertheless, we favoured steric hindrance originating from the phenylsulfone group.[9,10] In order to lend convincing support to our views, we considered studying new Michael acceptors in which the influence of electronic factors and steric effects are minimal. Such requirements were expected to be fulfilled by 4-fluorocyclohexa-2,5-dienones (e.g., **13**) (Scheme 2) because of the small size of the fluorine atom and its location at an sp^3 carbon atom. Moreover, we were keen to fabricate intermediates **7** and **8** by executing the annulation (Scheme 1) on the way to developing a methodology for the synthesis of angularly oxygenated AB ring angucyclines, for example, **9**,[11a] **10**[11b] and **11**[11c] (Fig. 1). Herein, we report that in the presence of LiO^{t}Bu, 4-fluorocyclohexa-2,5-dienones (e.g., **13**) readily react with 3-phenylsulfonylphthalides **1** to give a variety of anthraquinones (Table 1) in good yields.

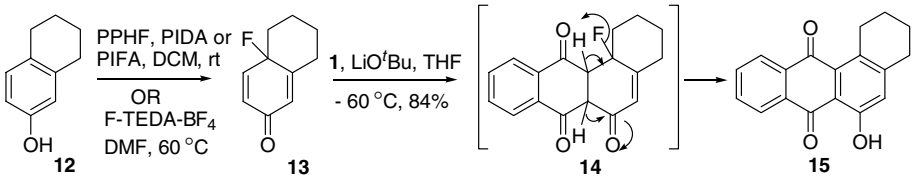
Alkyl-substituted 4-fluorocyclohexa-2,5-dienones are known in the literature,[12] and they can be easily pre-



Scheme 1. Proposed route to angularly oxygenated angucyclines.

* Corresponding author. E-mail: dmal@chem.iitkgp.ernet.in

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.01.159



Scheme 2.

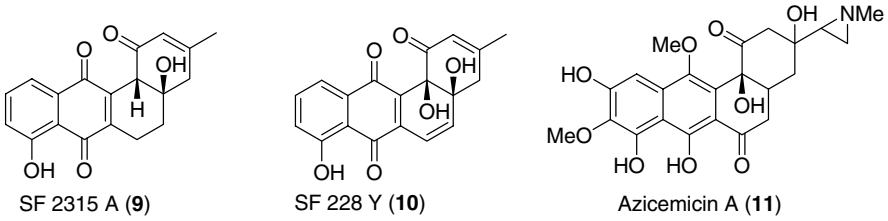


Figure 1. Structures of some angularly oxygenated angucyclines.

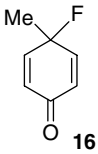
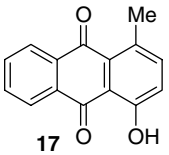
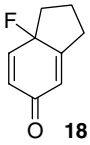
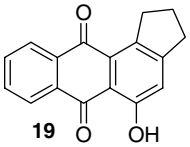
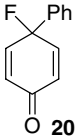
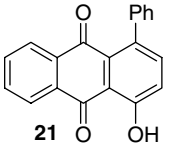
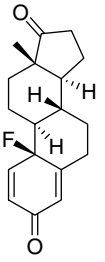
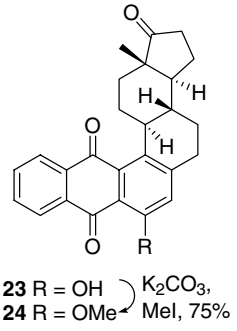
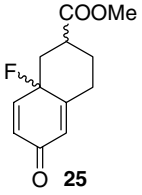
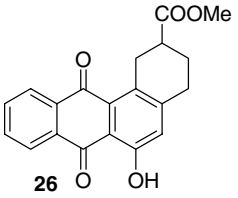
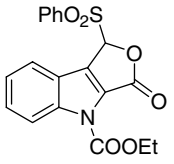
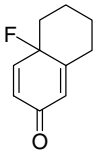
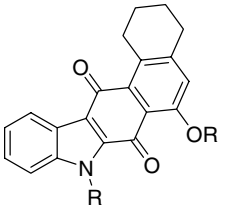
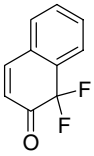
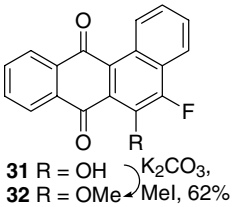
pared from the corresponding phenols by oxidative fluorination using pyridinium polyhydrogen fluoride (PPHF) and phenyliodonium bis-(trifluoroacetate) (PIFA)/phenyliodonium diacetate (PIDA)[13] or by electrophilic fluorination using Selectfluor F-TEDA-BF_4.[14] However, no study has so far been reported on their reactivity. The sole attempt on annulation of 4-fluoro-4-methoxy-2,5-cyclohexadienone only established its exceptional susceptibility to solvolysis.[15] On the other hand, 4-fluoro-5,6,7,8-tetrahydronaphthalen-2-one **13** is stable enough to be isolated and characterized. For the present study, compound **13** was prepared from 5,6,7,8-tetrahydro-2-naphthol **12** by oxidation with PPHF–PIDA, and then reacted with 3-phenylsufonylphthalide **1** in the presence of LiO^tBu at −60 °C. As anticipated, the reaction mixture turned deep red in colour with an increase in reaction temperature, indicating progress towards annulation.[16] Work-up of the reaction mixture afforded anthraquinone **15** (84%), the ^{1}H NMR data of which matched well with that reported.[10b] Attempted trapping of the immediate product of annulation, that is, **14**, by quenching the reaction with CH_3I had no effect on the product profile (Scheme 2). A similar reaction with 3-phenylsulfanylphthalide **3** yielded the same product **15** in a 72% yield. Although it was anticipated that the very high strength of the C–F bond would prevent elimination of fluorine and make the isolation of intermediate **14** feasible, the reaction led to eventual loss of the fluorine atom. Nevertheless, the results established that a 4-fluorocyclohexadienone was more reactive than the corresponding 4-methoxy analog: the methoxy derivative **4** did not react with sulfone phthalide **1**[10b,c] under similar conditions. The different reactivity of **4** and **13** towards **1** can unarguably be attributed to steric effect. The methoxy group at the ring junction in **4** would cause a neopentyl steric interaction (F-strain[17]) with the incoming anion of **1**. Such an interaction would be less in **13**, fluorine being a very small atom. Moreover, the electronic effects exerted by both F and OMe on the reaction centre will be of similar magnitude since they are both situated one carbon away.

For further evaluation of the reactivity of 4-fluorocyclohaxadienones, we prepared compounds **16** and **18** from *p*-cresol and 2-indanol, respectively, according to a known oxidation procedure[13] involving PPHF–PIDA. Their annulation with **1** gave the expected anthraquinones **17** and **19** in 79% and 77% yields, respectively, being comparable with those of the reactions with the 4-methoxy counterparts (Table 1, entries 1 and 2). A similar reaction of 4-fluoro-4-phenyl-2,5-cyclohexadienone **20**, prepared from 4-phenylphenol by oxidation with F-TEDA-BF_4, furnished **21** in a 78% yield, whereas the corresponding 4-methoxy derivative gave only a 41% yield of the product (Table 1, entry 3). Anticipating pronounced steric effects in naphthalenone acceptors, we proceeded to examine 10-β-fluoro-1,4-estradien-3,17-dione **22**[13,14] and 4-fluoro-6-methoxycarbonyl-5,6,7,8-tetrahydro-2-naphthalenone **25**. Their reactions with **1** furnished products **23** (68%) and **26** (89%), respectively. Understandably, their methoxy analogs did not undergo annulation (Table 1, entries 4 and 5).[18] Similarly, 1-phenylsulfonyl-3-furoindolone **27**, which was previously reported[19] not to react with methoxynaphthalenone **4**, gave indoloangucycline **28** in excellent yield (85%), when reacted with fluoro acceptor **13** (Table 1, entry 6).

The yields of the reactions of **13**, **18** and **20** with 3-cyanophthalide (**2**) were comparable to those with 3-phenylsulfonylphthalide (**1**). However, in the case of 1,1-difluoro-2-naphthalenone **30**,[14] annulation with **1** resulted in only a 27% yield of product **31**. With 3-cyanophthalide **2**, the yield of **31** increased to 61% (Table 1, entry 7).[20] The reason for the difference in the yields is currently unknown. For direct access to structure **8** (Scheme 1) we briefly examined the reactivity of 4-hydroxycyclohexa-2,5-dienone **5**, prepared in two steps from **12**.[21] However, it did not react with any of the Hauser donors **1**, **2** or **3** and in each case starting enone **5** was recovered.

In conclusion, we have demonstrated that readily accessible 4-fluorocyclohexa-2,5-dienones are reactive accep-

Table 1.

Entry	Phthalide	Enone	Annulated product	% Yield
1	**1**	 **16**	 **17**	79 76[a]
2	**1**	 **18**	 **19**	77 78[a] 78[c]
3	**1**	 **20**	 **21**	78 41[a] 80[c]
4	**1**	 **22**	 **23** R = OH, **24** R = OMe (K_2CO_3, MeI, 75%)	68 0[a] 51[b]
5	**1**	 **25**	 **26**	89 0[a]
6	 **27**	 **13**	 **28** R = H, **29** R = Me (K_2CO_3, MeI, 71%)	85 0[a]
7	**1**	 **30**	 **31** R = OH, **32** R = OMe (K_2CO_3, MeI, 62%)	27 10[b] 61[c]

[a] Yields refer to reactions with the corresponding 4-methoxycyclohexadienone acceptors.
[b] Yield refer to the reactions with **3**.
[c] Yield refers to the reaction with **2**.

tors for the Hauser annulation. With the successes described in entries 4, 6 and 7, we have established that the annulation with sulfonylphthalides can be extended to the synthesis of anthraquinone-steroid hybrids[22] (i.e., **23**), fused indoloquinones (i.e., **28**) and fluoroanalogs of angucyclines (i.e., **31**).

Acknowledgements

Financial support for this work was provided by the CSIR, New Delhi and the DST, New Delhi. P.P. gratefully acknowledges the receipt of his senior research fellowship from the CSIR, New Delhi.

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16. *Representative annulation procedure*: To a stirred solution of **1** (82 mg, 0.3 mmol) in THF (4 mL) at −60 °C (chloroform/liquid N_2 bath) under an inert atmosphere was added solid lithium *tert*-butoxide (72 mg, 0.9 mmol). The resulting yellowish solution was stirred at −60 °C for 15 min, after which a solution of **13** (50 mg, 0.3 mmol) in THF (2 mL) was added. The cooling bath was removed after about 30 min at −60 °C and the reaction mixture was brought to room temperature and further stirred for 2–3 h. The reaction was then quenched with 10% aqueous NH_4Cl solution (5 mL) and the residue diluted with ether (10 mL). The aqueous layer was extracted with ether (2 × 10 mL) and the combined organic layers were washed with H_2O (2 × 10 mL), brine (5 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel (10% ethyl acetate in petroleum ether).
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20. *Selected data*: Compound **23** (red solid): mp 205–207 °C; ν_{max} (KBr, cm^{-1}): 1735, 1635, 1272, 769; ^1H NMR ($CDCl_3$, 200 MHz): δ 12.88 (s, 1H), 8.26–8.12 (m, 2H), 7.80–7.73 (m, 2H), 7.02 (s, 1H), 3.49–3.41 (m, 1H), 3.10–2.75 (m, 1H), 2.60–2.45 (m, 1H), 2.25–1.10 (m, 12H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 220.2, 188.7, 186.6, 160.4, 149.8, 137.9, 135.2, 134.6, 133.8, 133.5, 132.2, 127.2, 126.2, 123.3, 116.3, 50.4, 48.6, 46.3, 40.3, 36.0, 35.8, 32.4, 30.6, 23.9, 21.5, 14.5; HRMS ESI: for $C_{26}H_{25}O_4$ $[M+H]^+$ calcd. 401.1753, found 401.1720. Compound **25** (light yellow liquid): ν_{max} (KBr, cm^{-1}): 2954, 1735, 1677, 1436, 1068, 883; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.80 (dd, 1H, $J = 10.1$, 6.2 Hz), 6.24 (dt, 1H, $J = 10.1$, 1.5 Hz), 6.08 (s, 1H), 3.70 (s, 3H), 3.10–2.85 (m, 2H), 2.80–2.45 (m, 3H), 2.40–2.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 185.2 (d, $J = 4.9$ Hz), 174.0, 156.4 (d, $J = 18.7$ Hz), 144.7 (d, $J = 21.0$ Hz), 129.8 (d, $J = 7.6$ Hz), 124.6 (d, $J = 4.6$ Hz), 86.6 (d, $J = 164.4$ Hz), 52.1, 39.7 (d, $J = 24.6$ Hz), 37.9, 30.7, 29.6; HRMS ESI: for $C_{12}H_{14}FO_3$ $[M+H]^+$ calcd. 225.0927, found 225.0907; for $C_{10}H_{10}FO$ $[M-COOMe]^+$ calcd. 165.0716, found 165.0672. Compound **29** (yellow solid): mp 173–175 °C; ν_{max} (KBr, cm^{-1}): 1650, 1584, 1240, 973, 752; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.41 (d, 1H, $J = 7.3$ Hz), 7.50–7.26 (m, 3H), 6.97 (s, 1H), 4.20 (s, 3H), 3.99 (s, 3H), 3.50–3.30 (m, 2H), 3.00–2.75 (m, 2H), 1.90–1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 184.4, 179.7, 174.7, 158.3, 147.4, 139.3, 135.4, 134.0, 133.7, 126.5, 123.8, 123.6, 120.9, 118.5, 118.1, 110.5, 56.3, 31.9, 29.7, 28.9, 23.5, 21.9; HRMS ESI: for $C_{22}H_{20}NO_3$ $[M+H]^+$ calcd. 346.1443, found 346.1405. Compound **31** (red solid): mp 205–207 °C; ν_{max} (KBr, cm^{-1}): 1648, 1570, 1340, 952, 759; ^1H NMR ($CDCl_3$, 200 MHz): δ 12.52 (s, 1H), 9.60 (d, 1H, $J = 8.2$ Hz), 8.30–8.22 (m, 2H), 8.10–8.05 (m, 1H), 7.85–7.75 (m, 2H), 7.65–7.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.1, 184.1, 149.7 (d, $J = 258.9$ Hz), 143.6 (d, $J = 12.7$ Hz), 135.3, 134.8, 133.5, 131.7, 129.6 (d, $J = 3.1$ Hz), 128.7, 128.4 (d, $J = 2.2$ Hz), 128.1, 127.9 (d, $J = 22.2$ Hz), 127.4, 126.4, 125.2, 120.6 (d, $J = 4.3$ Hz), 119.4 (d, $J = 6.6$ Hz); HRMS ESI: for $C_{18}H_{10}FO_3$ $[M+H]^+$ calcd. 293.0614, found 293.0583.
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