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A Novel Synthesis of Substituted Naphthalenes

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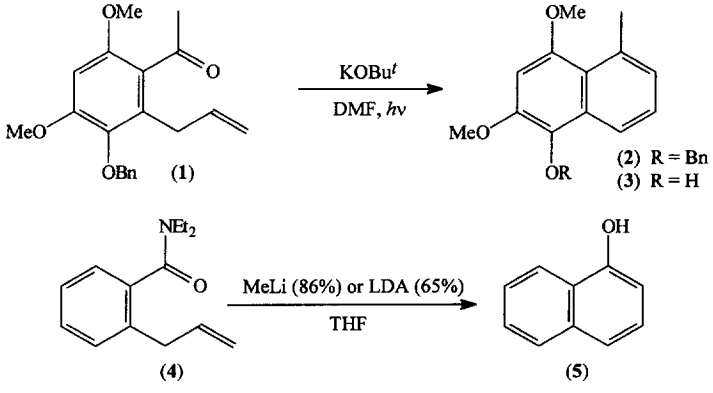
Abstract: Irradiation of 2-allylated acylbenzenes in DMF in the presence of potassium *tert*-butoxide constitutes a novel synthesis of substituted naphthalenes, including arylnaphthalenes. Typical examples include the conversions **(1)** → **(2)**, **(8)** → **(11)** and **(15)** → **(16)**.

Natural products that contain a naphthalene nucleus often exhibit biological activity[1]. As a result there is much interest in their synthesis[2]. When the napthalene nucleus bears aromatic substituents[3], restricted rotation (atropisomerism) about the biaryl axes may influence their biological activity. This structural feature brings a new dimension to the synthesis of arenes, and the challenge has been met in various ingenious ways[4,5]. In this paper we describe a novel method for the regiospecific construction of highly substituted naphthalenes, including naphthalenes containing biaryl axes.

In attempting to bring the double bond of 2-allyl-3-benzyloxy-4,6-dimethoxyacetophenone[6] **(1)** into conjugation by isomerization with potassium *tert*-butoxide in dimethylformamide (DMF) according to a reported procedure[7], we have observed unexpected cyclization to give the naphthalene **(2)**. The structure of the product was confirmed by catalytic hydrogenolysis of the benzyl group (1 atm H_2, 10% Pd/C) to afford the naphthol **(3)**, the spectrosopic evidence for which was incontestable[8]. Examination of the literature revealed a similar transformation, *viz.* **(4)** → **(5)**, published by Snieckus[9]; his reaction differs from ours in producing a *naphthol* rather than a *naphthalene*. Interestingly, exposure to light appeared to influence the outcome of our reaction; in fact, our best yield for the conversion of **(1)** into **(2)** (56%) was achieved upon irradiating the reaction mixture with a high pressure mercury lamp (400W) at *ca* 80°C, and in the presence of four mole equivalents of potassium *tert*-butoxide. The implication is that the mechanism of our transformation might be quite different from that operating in the Snieckus example. We therefore decided to investigate the scope of what seemed to be a novel synthesis of naphthalenes.



The first set of experiments was performed with a variety of 2-allylated benzaldehydes (**8**), prepared in three steps from isovanillin (**6**) (see Table 1). Alkylation of (**6**) with allyl bromide or various substituted allyl bromides (DMF, K_2CO_3, 60°C) gave the corresponding allyl ethers (**7a-d**) in high yields. Heating the allyl ethers in DMF at 170°C induced Claisen rearrangement, after which the resulting phenols were protected as the isopropyl ethers (**8a-c**). With the cinnamyl ether (**7d**), the product of this series of reactions was the styrene (**9**) rather than the allylbenzene. Furthermore, when the Claisen rearrangement was performed on the crotyl ether (**7b**) in the absence of solvent, a separable mixture of the Claisen product (**8b**) (38%) and the alternative product (**10**) (34%), was isolated after treatment with isopropyl bromide. Product (**10**) probably arises from Claisen rearrangement to the alternative *ortho* position followed by Cope rearrangement.

When substrates (**8a-c**) and (**9**) were irradiated in *dry* DMF in the presence of four mole equivalents of potassium *tert*-butoxide in a quartz vessel[10], the desired naphthalenes (**11a-d**) were obtained in good yields (Table 1). It should be noted that product (**11d**) is a naphthalene which possesses a biaryl axis. With substrate (**10**), the naphthalene (**12**) was isolated in much lower yield (33%), suggesting that an ether substituent *ortho* to the allylic chain may facilitate the cyclization.

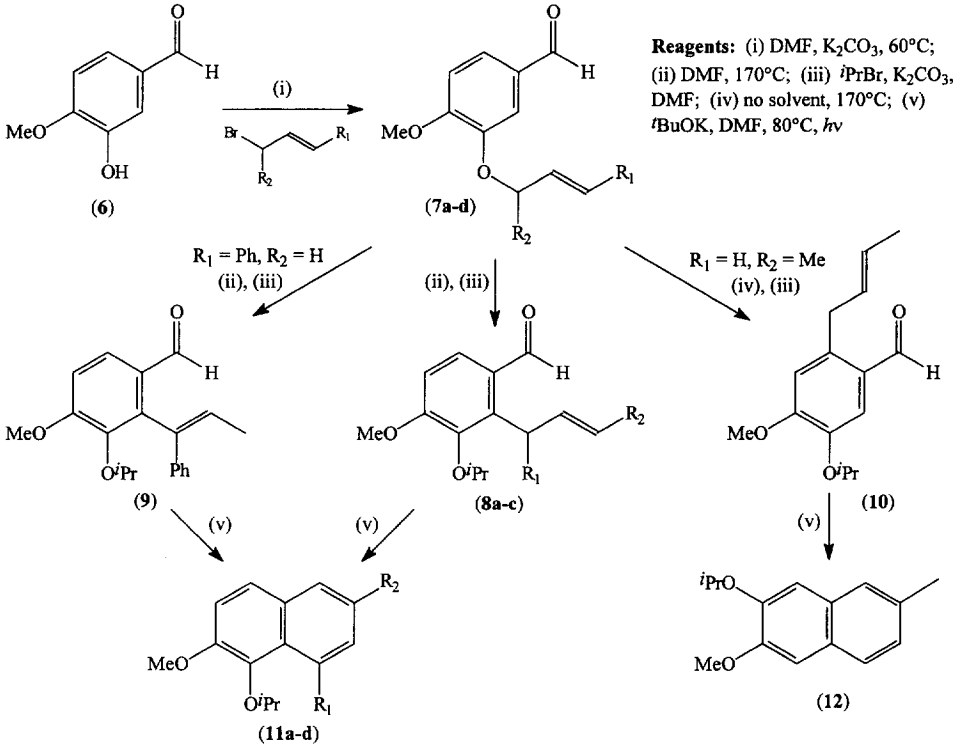
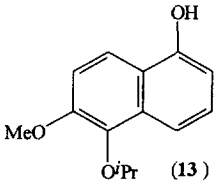


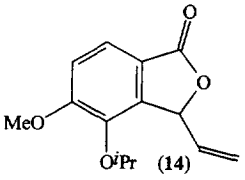
Table 1: Yields for the reaction sequence (**6**) → (**7**) → (**8**)/(**9**) → (**11**)[8]

Substituents	Allyl ethers (**7**)	Claisen products	Naphthalenes (**11**)
a $R_1 = R_2 = H$	99%	(**8a**), 93%	81%
b $R_1 = Me$, $R_2 = H$	93%	(**8b**), 68%	61%
c $R_1 = H$, $R_2 = Me$	90%	(**8c**), 87%	68%
d $R_1 = Ph$, $R_2 = H$	85%	(**9**), 51%	82%

During the course of our investigations on this series of substrates, transformation **(8a)** → **(11a)** was studied extensively. It was noted that if the DMF was not freshly distilled and dried, or if the reaction was performed with insufficient base, the yield of the desired naphthalene decreased and two additional side products were isolated in yields of 2-3%. These were characterized as the related naphthol **(13)** and the 3-vinyl phthalide **(14)**[8].

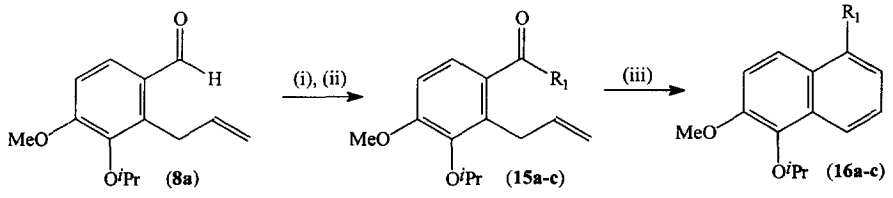


(13)



(14)

We next turned our attention to varying the groups present at the carbonyl centre. Since it had earlier been demonstrated that the methyl ketone **(1)** could undergo the novel reaction **(1)** → **(2)**, we wanted to examine the possibility of utilizing substituted benzophenones for making 1-arylnaphthalenes. The three substrates **(15a-c)** were synthesized by treatment of aldehyde **(8a)** with suitable aryllithiums, after which the intermediate alcohols were oxidized with manganese(IV) oxide (Table 2). Applying our cyclization conditions to these substituted benzophenones afforded the desired biaryl products **(16)** in moderate to good yields.



Reagents: (i) ArLi, THF, -78°C; (ii) MnO_2, benzene, 25°C; (iii) ^tBuOK, DMF, 80°C, *hv*.

Table 2: Yields for the reaction sequence **(8a)** → **(15)** → **(16)**

Entry	Ketones (15)	Naphthalenes (16)
a R_1 = Ph	80%	79%
b R_1 = 1-Naphthyl	77%	71%
c R_1 = 3,4-$(MeO)_2C_6H_3$	68%	37%

The mechanism of this novel reaction is under investigation. It seems feasible to suggest initial photoenolization[11], followed by electrocyclic ring closure and base-induced elimination of water. However, mechanisms involving radical intermediates cannot be ruled out at this stage, especially since precedents exist for single-electron transfer from alkoxide bases[12]. Full results will be reported in a later publication, together with studies on the use of alternative bases and solvents.

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8. All new compounds were characterised spectroscopically and by elemental analysis or high resolution mass spectrometry. Spectroscopic data for some selected compounds:
   1-Isopropoxy-2-methoxynaphthalene (**11a**). (Found M^+, 216.1151. $C_{14}H_{16}O_2$ requires M, 216.1150); ν_{max}/cm^{-1} ($CHCl_3$) 1626, 1596 and 1573; δ_H ($CDCl_3$) 1.35 (6H, d, *J* 6.1 Hz, $CH(CH_3)_2$), 3.91 (3H, s, OCH_3), 4.64 (1H, sept, *J* 6.1 Hz, $CH(CH_3)_2$), 7.23 (1H, d *J* 8.9 Hz, 3-H), 7.33 (1H, ddd, *J* 8.2, 6.8 and 1.2 Hz, 6-H), 7.43 (1H, ddd, *J* 8.4, 6.8 and 1.2 Hz, 7-H) 7.53 (1H, d *J* 8.9 Hz, 4-H), 7.72 (1H, dd, *J* 8.2 and 1.2 Hz, 5-H) and 8.15 (1H, dd, *J* 8.4 and 1.2 Hz, 8-H); δ_C ($CDCl_3$) 22.68 ($CH(CH_3)_2$), 56.77 (OCH_3), 75.25 ($CH(CH_3)_2$), 115.32 (C-6), 122.14 (C-8), 123.64 (C-4), 123.85 (C-3), 125.64 (C-7), 127.41 (C-5), 129.69 (C-4a), 130.38 (C-8a), 140.90 (C-1) and 148.50 (C-2); *m/z* 216 (M^+, 38%), 174 (100), 169 (91), 131 (29) and 77 (12).
   4-Isopropoxy-5-methoxy-3-vinylphthalide (**14**). (Found M^+, 248.1035. $C_{14}H_{16}O_4$ requires M, 248.1048); ν_{max}/cm^{-1} ($CHCl_3$) 1763, 1610 and 1597; δ_H ($CDCl_3$) 1.26 and 1.31 (each 3H, 2xd, *J* 6.1 Hz, $CH(CH_3)_2$), 3.94 (3H, s, OCH_3), 4.68 (1H, sept, *J* 6.1 Hz, $CH(CH_3)_2$), 5.34 (1H, ddd, *J* 10.3, 1.2 and 1.1 Hz, $=CH_aH_b$), 5.57 (1H, ddd, *J* 17.1, 1.2 and 1.1 Hz, $=CH_aH_b$), 5.83 (1H, br d, *J* 6.1 Hz, 3-H), 6.01 (1H, ddd, *J* 17.1, 10.3 and 6.1 Hz, $-CH=CH_2$), 7.06 (1H, d, *J* 8.3 Hz, 6-H) and 7.60 (1H, d, *J* 8.3 Hz, 7-H); δ_C ($CDCl_3$) 22.60 and 22.72 ($CH(CH_3)_2$), 56.34 (OCH_3), 74.81 ($CH(CH_3)_2$), 80.03 (C-3), 114.02 (C-6), 118.45 ($-CH=CH_2$), 118.70 (C-7a), 121.52 (C-7), 132.45 ($-CH=CH_2$), 141.09 (C-4), 141.82 (C-3a), 157.43 (C-5) and 169.94 (C-1); *m/z* 248 (M^+, 20%), 206 (100), 179 (32) and 151 (73).
9. Sibi, M.P.; Dankwardt, J.W.; Snieckus, V. *J. Org. Chem.* **1986**, *51*, 271-273.
10. Typical experimental procedure: A solution of the carbonyl-containing compound (150-300 mg) in dry DMF (20-40 cm^3) was heated to 70-80°C. Potassium *tert*-butoxide (4 mole equivalents) was added and heating was maintained for 10-20 minutes with concomitant irradiation from a 400W high pressure mercury lamp through a quartz filter. Water (20-40 cm^3) was added, and the mixture was acidified with dilute aqueous HCl. The solution was extracted with several portions of diethyl ether, after which the organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed (SiO_2, 5-30% ethyl acetate/hexane) to afford the desired products in yields of 33-82%.
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