Synthesis of 2-Benzylphenols: Transformation of the Baylis-Hillman Adducts Derived from 2-Cyclohexen-1-one

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Recently, we have reported on the novel synthesis of quinoline derivatives from the Baylis-Hillman adducts.[1,2] As an extension of the reaction, we intended to prepare acridine skeleton from the Baylis-Hillman adducts of 2-cyclohexen-1-one as shown in Scheme 1. However, we could not prepare the desired compounds *via* the reaction scheme (*vide infra*). Instead, we could obtain 2-benzylphenol derivatives in good yields as shown in Scheme 2 and wish to report herein the results.

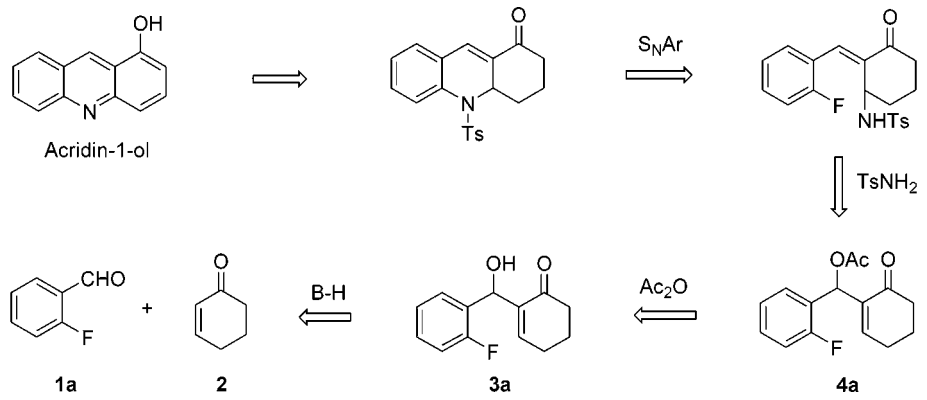
The Friedel-Crafts alkylation reaction is one of the most powerful methods to form the carbon-carbon bond in organic reactions. The Friedel-Crafts benzylation reaction is of great synthetic significance in industrial processes.[3] However, synthesis of 2-benzylphenols regioselectively from phenols or benzyl phenyl ethers is difficult due to the formation of *ortho-*/*para-* mixtures.[4] Synthesis of these compounds by Fries rearrangement of phenyl phenylacylates also suffers from the formation of mixtures.[5] *Ortho*-specific alkylation of phenols *via* 1,3,2-benzodioxaborins was known.[6] 1,3,2-Benzodioxaborins can be reduced to *ortho*-alkyl phenols with *tert*-butylamine borane in the presence of aluminum chloride.

The Baylis-Hillman reaction of 2-fluorobenzaldehyde (**1a**) and 2-cyclohexen-1-one (**2**) was carried out in aqueous THF with the aid of DMAP at room temperature to give the corresponding adduct **3a** in 58% yield as reported previously.[7] Acetylation of **3a** with Ac_2O/DMAP gave **4a** in 91% yield. Initially, we examined the reaction of **4a** and *p*-toluenesulfonamide in the presence of K_2CO_3 in DMF. However, 2-(2-fluorophenyl)methylphenol (**5a**) was isolated in 74% yield, unexpectedly. The formation of **5a** occurred well without tosylamide. Actually, the yield of **5a** was improved up to 94% without tosylamide as shown in Table 1 (entry 1).

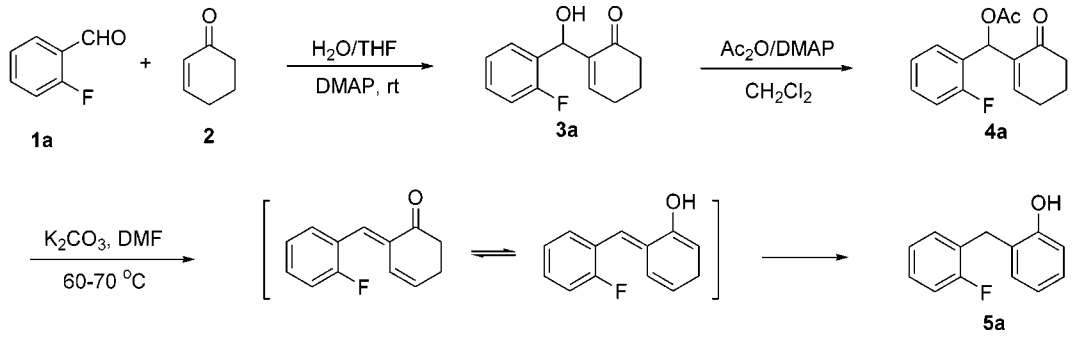
Thus, we prepared some Baylis-Hillman acetates of 2-cyclohexen-1-one and examined their conversion to 2-arylmethylphenols and the results are summarized in Table 1. As mentioned previously, the Baylis-Hillman reaction of **1** and **2** was carried out in aqueous THF in the presence of 0.1 equiv. of DMAP.[7] The corresponding adducts **3a-h** were obtained in reasonable yields (41-64%) at room temperature. Following conversion to their acetate **4a-h** was excellent in all cases (CH_2Cl_2, Ac_2O/DMAP, rt, 90-98%). The reaction of **4a-f** in DMF in the presence of K_2CO_3 (1.0 equiv) gave **5a-f** in good yields (89-96%) in short time (1-2 h) at 60-70 ^oC.[8] The formation of **5g**, the quinoline derivative, was carried out at room temperature. The reaction is believed to occur as depicted in Scheme 2: potassium carbonate assisted elimination of acetic acid and the following keto-enol tautomerization and 1,5-hydrogen transfer.[9]

We could not obtain the corresponding phenol derivative from the analogous reaction with **4h**, derived from hexanal. Intractable mixtures were observed on tlc at 60-70 ^oC. Instead, we could isolate cyclohexenone derivative **6** in 40% yield at room temperature.[10] The structure of **6** was determined by ^1H, ^{13}C, and ^1H-^1H COSY.[8]

In conclusion we disclosed unusual transformation of the Baylis-Hillman acetates of 2-cyclohexen-1-one into 2-arylmethylphenols. Further chemical transformation of the products to xanthene derivatives *via* the nucleophilic aromatic substitution strategy and the synthesis of acridines are underway.

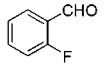
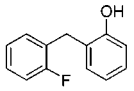
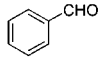
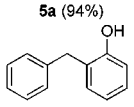
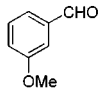
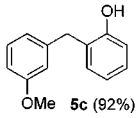
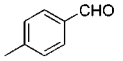
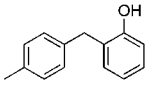
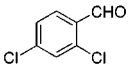
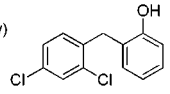
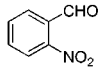
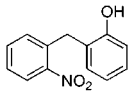
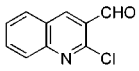
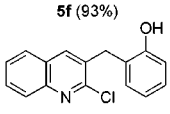
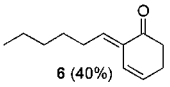


Scheme 1



Scheme 2

Table 1. Synthesis of 2-benzylphenols **5**

Entry	Aldehyde **1**	**3a-h**	**4a-h**	Conditions	Product
1		**3a** (58%)[7]	**4a** (91%)	K_2CO_3 (1.0 equiv) DMF, 60-70 °C 1 h	 **5a** (94%)
2		**3b** (55%)[7]	**4b** (90%)	K_2CO_3 (1.0 equiv) DMF, 60-70 °C 2 h	 **5b** (89%)
3		**3c** (63%)[7]	**4c** (96%)	K_2CO_3 (1.0 equiv) DMF, 60-70 °C 2 h	 **5c** (92%)
4		**3d** (41%)	**4d** (92%)	K_2CO_3 (1.0 equiv) DMF, 60-70 °C 1 h	 **5d** (96%)
5		**3e** (53%)[7]	**4e** (96%)	K_2CO_3 (1.0 equiv) DMF, 60-70 °C 1 h	 **5e** (95%)
6		**3f** (56%)[7]	**4f** (98%)	K_2CO_3 (1.0 equiv) DMF, 60-70 °C 2 h	 **5f** (93%)
7		**3g** (53%)[7]	**4g**(97%)	K_2CO_3 (1.0 equiv) DMF, rt 6 h	 **5g** (61%)
8	$CH_3(CH_2)_4CHO$	**3h** (64%)[7]	**4h** (98%)	K_2CO_3 (1.0 equiv) DMF, rt 20 h	 **6** (40%)

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4. Regioselective synthesis of 2-benzylphenols from benzyl phenyl ether was achieved by using K10-montmorillonite, see Venkatachalapathy, C.; Pitchmamani, K.; Sivasultramanian, S. *Indian J. Chem.* **1998**, *37B*, 301. For the synthesis of 2-benzylphenol from the benzylation of the dianion of *o*-cresol, see Bates, R.; Siahaan, T. J. *J. Org. Chem*. **1986**, *51*, 1432.
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6. Lau, C. K.; Williams, H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Belanger, P. C. *Can. J. Chem*. **1989**, *67*, 1384.
7. Lee, K. Y.; Gong, J. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2002**, *23*, 659.
8. Representative spectroscopic data of **5a** is as follows: oil; ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 2H), 4.88 (br s, 1H), 6.75-7.15 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 28.82 (d, J = 2.9 Hz), 115.21 (d, J = 22.0 Hz), 115.58, 121.02, 124.11 (d, J = 3.3 Hz), 125.76, 126.96 (d, J = 15.8 Hz), 127.86, 127.99, 130.78, 130.84, 153.51, 160.99 (d, J = 244.7 Hz); Mass (70 eV) *m/z* (rel. intensity) 78 (14), 106 (30), 152 (15), 181 (41), 183 (36), 202 (M^+, 100). Representative spectroscopic data of **6** is as follows: oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3H), 1.27-1.34 (m, 4H), 1.43-1.50 (m, 2H), 2.22 (q, J = 7.5 Hz, 2H), 2.49-2.61 (m, 4H), 5.99-6.03 (m, 1H), 6.54-6.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.93, 22.44, 24.40, 27.25, 28.38, 31.52, 38.20, 123.99, 128.34, 131.79, 136.64, 199.49.
9. We examined the synthesis of **5a** from **3a** by direct dehydration. The reaction of **3a** in benzene in the presence of *p*-TsOH showed the formation of complex mixtures. For the synthesis of similar 2-arylmethylphenols by direct dehydration in acidic medium in low yields, see (a) Patra, A.; Batra, S.; Joshi, B. S.; Roy, R.; Kundu, B.; Bhaduri, A. P. *J. Org. Chem*. **2002**, *67*, 5783. (b) Iwamura, T.; Fujita, M.; Kawakita, T.; Kinoshita, S.; Watanabe, S.-i.; Kataoka, T. *Tetrahedron* **2001**, *57*, 8455.
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