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# One-pot inter- and intramolecular Friedel–Crafts reactions in Baylis–Hillman chemistry: a novel facile synthesis of (*E*)-2-arylideneindan-1-ones

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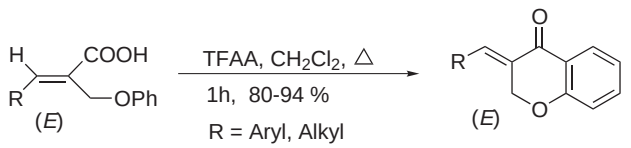
**Abstract**—A simple one-pot stereoselective transformation of *tert*-butyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis–Hillman adducts obtained from *t*-butyl acrylate, into (*E*)-2-arylideneindan-1-ones involving one inter- and one intramolecular Friedel–Crafts reaction is described. 

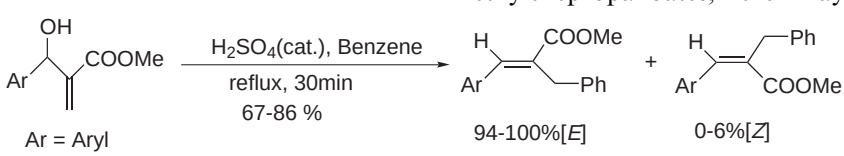
The Baylis–Hillman reaction is an emerging atom economic reaction producing an interesting class of densely functionalized molecules whose applications in a variety of stereoselective processes have been well documented in the literature.[1–10] We recently described the sulfuric acid catalyzed (intermolecular) Friedel–Crafts reaction of the Baylis–Hillman adducts, i.e. methyl 3-aryl-3-hydroxy-2-methylenepropanoates with benzene providing a simple stereoselective synthesis of methyl (2*E*)-3-aryl-2-benzylprop-2-enoates (Eq. (1)).[7,11] We have also described an intramolecular Friedel–Crafts reaction of (2*E*)-2-aryloxymethylalk-2-enoic acids under the influence of trifluoroacetic anhydride (TFAA) thus providing a simple synthesis of (*E*)-3-arylidene(or alkylidene)chroman-4-ones (Eq. (2)).[8] We wanted to design a simple methodology to carry out both inter- and intramolecular Friedel–Crafts reactions on the Baylis–Hillman adducts in an operationally simple one-pot procedure. Thus we report a convenient one-pot synthesis of (*E*)-2-arylideneindan-1-ones from *tert*-butyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis–Hillman adducts obtained from *tert*-butyl acrylate,[12] essentially involving one inter- and one intramolecular Friedel–Crafts reaction in a one-pot operation.




(2)

(*E*)-2-Arylideneindan-1-ones are useful synthons in the synthesis of various carbocyclic and heterocyclic molecules of biological importance.[13–20] The classical methods for the preparation of these important compounds involve the initial synthesis of the indan-1-one moiety, followed by aldol reaction with appropriate aldehydes.[13–17,20–22] To the best of our knowledge, there is no report in the literature first involving the synthesis of arylidene moiety and then construction of the indan-1-one framework for the preparation of (*E*)-2-arylideneindan-1-ones. We therefore felt that the development of a simple and efficient methodology for the stereoselective synthesis of the (*E*)-2-arylideneindan-1-one skeleton by preparing an (*E*)-arylidene moiety first and then constructing the indan-1-one framework would be of high importance.

It occurred to us that *tert*-butyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis–Hillman adducts




(1)

*Keywords*: Baylis–Hillman chemistry; inter- and intramolecular Friedel–Crafts reactions; 2-arylideneindan-1-ones; stereoselective transformations.
* Corresponding author.

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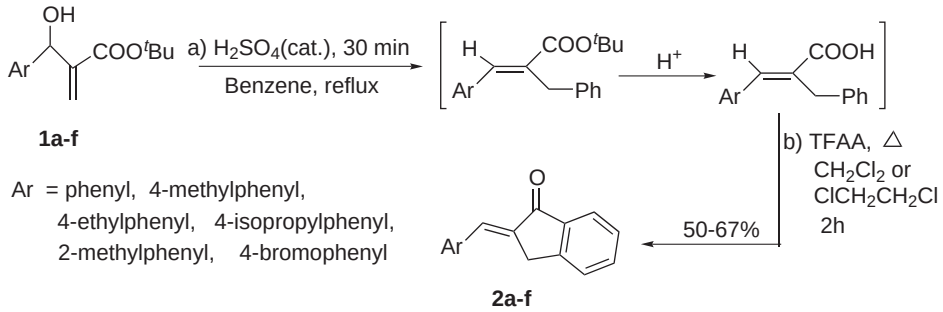
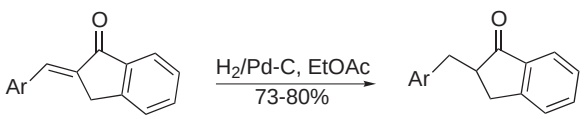



**Scheme 1.**

obtained from *tert*-butyl acrylate, might be appropriate substrates for the intermolecular Friedel–Crafts reaction with benzene under the catalytic influence of sulfuric acid. At the same time, sulfuric acid might cleave the *tert*-butyl ester to provide the corresponding cinnamic acid (through $A_{AL}1$ mechanism),[23] which might subsequently undergo intramolecular Friedel–Crafts cyclization under the influence of a suitable reagent to provide the required (*E*)-2-arylideneindan-1-ones. We also envisioned that all three steps could be carried out in one-pot.

Accordingly, we have first selected *tert*-butyl 3-hydroxy-3-phenyl-2-methylenepropanoate (**1a**) as a substrate for study. We have indeed achieved a fascinating result. Thus, treatment of **1a** (1 mM) with a catalytic amount of conc. $H_2SO_4$ (0.4 mM) in benzene (5 mL) at reflux for 30 min, followed by reaction with trifluoroacetic anhydride (TFAA) (2 mM) in dichloromethane (5 mL) (after removal of the solvent benzene under reduced pressure) for 2 h at reflux provided the desired 2-benzylideneindan-1-one (**2a**) in 63% yield after usual work-up and column chromatography (silica gel, 5% EtOAc in hexanes), followed by crystallization from chloroform and hexanes (2:3).[24] Encouraged by this result, we have prepared a representative class of (*E*)-2-arylideneindan-1-ones (**2b–f**) in 50–67% yields from representative Baylis–Hillman adducts (**1b–f**) derived from *tert*-butyl acrylate (Scheme 1, Table 1).

With a view to transforming these (*E*)-2-arylideneindan-1-ones into the corresponding 2-arylmethylindan-1-ones, another interesting class of organic molecule, we have subjected the molecules **2a–d** to catalytic hydrogenation in the presence of 5% Pd/C catalyst (40 psi) to afford the desired molecules **3a–d** (Eq. (3)).[25]




(3)

Ar = phenyl, 4-methylphenyl,
4-ethylphenyl, 4-isopropylphenyl

In conclusion, we have successfully, for the first time, developed an operationally simple procedure for conducting both inter- and intramolecular Friedel–Crafts reactions in one-pot to provide a simple methodology for the synthesis of (*E*)-2-arylideneindan-1-ones from the Baylis–Hillman adducts obtained from *tert*-butyl acrylate, thus demonstrating the applications of Baylis–Hillman chemistry in organic synthesis.

**Table 1.** Synthesis of (*E*)-2-arylideneindan-1-ones[a,b]

| Substrate | Ar | Product | Yield (%)[c] |
|---|---|---|---|
| **1a** | Phenyl | **2a** | 63 |
| **1b** | 4-Methylphenyl | **2b**[d] | 61 |
| **1c** | 4-Ethylphenyl | **2c**[d,e] | 59 |
| **1d** | 4-Isopropylphenyl | **2d** | 56 |
| **1e** | 2-Methylphenyl | **2e**[f] | 67 |
| **1f** | 4-Bromophenyl | **2f**[d,f] | 50 |

[a] All reactions were carried on 1 mM scale of Baylis–Hillman adducts (**1a–f**) with benzene (5 mL) in the presence of conc. $H_2SO_4$ (0.4 mM) at reflux for 30 min. Benzene solvent was removed under reduced pressure and the residue (resulting cinnamic acids) was treated with TFAA (2 mM, 0.28 mL) in $CH_2Cl_2$ at reflux for 2 h.

[b] All the products were obtained as yellow crystalline solids and gave satisfactory IR, $^1$H NMR (200 MHz), $^{13}$C NMR (50 MHz) spectral data and elemental analyses.

[c] Isolated yields of the pure products after column chromatography (silica gel, 5% EtOAc in hexanes) followed by crystallization (chloroform and hexanes, 2:3).

[d] $^1$H NMR of the crude products (**2b**, **2c** and **2f**) indicates the presence of small amounts ($\approx$5–15%) of the corresponding (*Z*)-isomer.[26]

[e] Structure was also confirmed by mass spectral analysis.

[f] Intramolecular Friedel–Crafts reactions were carried out in 1,2-dichloroethane as solvent at 50°C as these reactions are slow in dichloromethane at reflux.

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11. Recently Kim and co-workers have reported the Friedel–Crafts reaction of Baylis–Hillman adducts of *N*-tosylimine derivatives under the influence of sulfuric acid. See Ref. 9.
12. The Baylis–Hillman coupling of aryl aldehydes with *tert*-butyl acrylate catalyzed by DABCO is a slow process.[3] We have recently developed a faster reaction method for this purpose in silica gel solid-phase medium. The molecules (**1a**–**f**) were made following this procedure. Basavaiah, D.; Mallikarjuna Reddy, R. *Indian J. Chem. Sect. B*, in press.
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24. **Spectral data for 2a**: mp 109–110°C (lit.[14,17,27] 111°C); IR (KBr): 1693, 1624 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 4.05 (s, 2H), 7.32–7.76 (m, 9H), 7.91 (d, 1H, $J=7.6$ Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 32.26, 124.19, 126.05, 127.49, 128.78, 129.50, 130.55, 133.66, 134.44, 134.65, 135.26, 137.86, 149.50, 193.99; elemental anal. calcd for $C_{16}H_{12}O$: C, 87.25; H, 5.49 and found C, 87.36; H, 5.47.
25. **Spectral data for 3a**: IR (neat): 1711, 1608 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.58–3.48 (m, 5H), 7.15–7.61 (m, 8H), 7.78 (d, 1H, $J=7.4$ Hz); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 32.22, 36.99, 48.93, 124.00, 126.34, 126.57, 127.41, 128.52, 128.89, 134.76, 136.61, 139.65, 153.58, 207.62; elemental anal. calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35 and found C, 86.72; H, 6.30.
26. $^1H$ NMR chemical shift values of β-vinylic proton and benzylic methylene protons of both (*E*)- and (*Z*)-isomers of 2-arylideneindan-1-ones (aryl group = phenyl, 4-methylphenyl, 4-methoxyphenyl and 4-chlorophenyl) have been reported.[28] The β-vinylic proton of (*Z*)-isomers appears at $\approx\delta$ 6.87–6.96 while that of (*E*)-isomers is hidden by the aromatic protons. The benzylic methylene protons of (*Z*)-isomers appear at $\approx\delta$ 3.81–3.87 while that of (*E*)-isomers appear at downfield, i.e. $\approx\delta$ 3.94–4.02.[28] In comparison to these literature values, singlets with low intensities at $\delta$ 7.00 and 3.91 ($\approx$12%, **2b**), $\delta$ 7.01 and 3.89 ($\approx$5%, **2c**) and $\delta$ 6.94 and 3.90 ($\approx$15%, **2f**) in $^1H$ NMR spectra of the crude products of **2b**, **2c** and **2f** are assigned to β-vinylic and benzylic protons, respectively, of the corresponding minor (*Z*)-isomers. The singlets at $\delta$ 4.05 ($\approx$88%, **2b**), $\delta$ 4.04 ($\approx$95%, **2c**) and $\delta$ 4.02 ($\approx$85%, **2f**) were assigned to benzylic methylene protons of the corresponding major (*E*)-isomers.
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