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An expedient synthesis of 2-substituted naphthalenes from the Baylis–Hillman adducts

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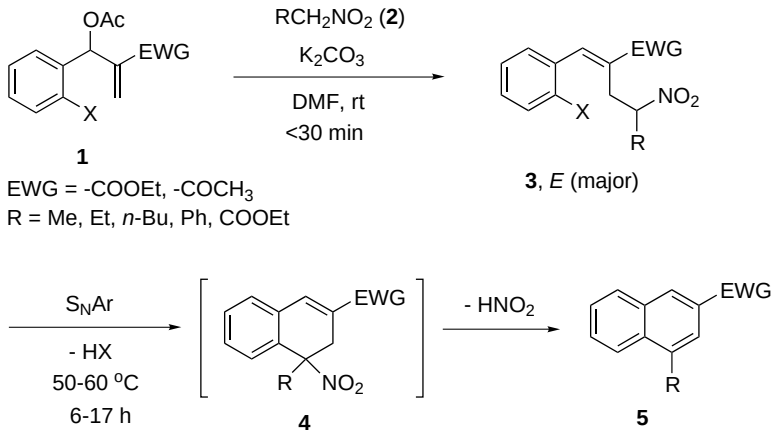
Abstract—The reaction of **1**, the acetates of the Baylis–Hillman adducts, and primary nitroalkanes **2** in the presence of potassium carbonate in *N*,*N*-dimethylformamide afforded 2-substituted naphthalenes **5** in good yields.

The Baylis–Hillman reaction is well known as a coupling reaction of aldehydes and activated alkenes catalyzed by tertiary amines or tertiary phosphines.[1] The reaction with ethyl acrylate serves α-methylene-β-hydroxy esters, which have been transformed into various useful compounds.[2]

Much attention has recently been focused on the regioselective synthesis of substituted naphthalene derivatives.[3] Since these compounds have the basic skeleton of many biologically important natural products and pharmaceuticals,[4] synthetic methods for the naphthalene moiety are highly desired.

In the course of our studies on the chemical transformation of the Baylis–Hillman adducts,[5] we intended to develop a method for the preparation of naphthalene skeleton by using the Baylis–Hillman adducts. Our rational design was depicted in Scheme 1: (1) S_N2'-type reaction of nitronate anion, which was generated from primary nitroalkane **2**, to the Baylis–Hillman acetate **1**; (2) intramolecular S_NAr reaction of **3**; (3) elimination of nitrous acid from the 1,2-dihydronaphthalene derivative **4** to give the desired naphthalene **5**.

Conjugate addition of nitroalkane to allyl Baylis–Hillman acetates in the presence of NaOH was recently reported by Amri et al,[6] who have prepared (*E*)-2-alkylidene-1,4-diketones via the Nef reaction of the initially obtained conjugate addition products. Intermolecular S_NAr reaction of nitronate to nitrobenzenes



Scheme 1.

Keywords: Baylis–Hillman adducts; 2-substituted naphthalenes; nitroalkanes.

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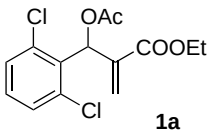
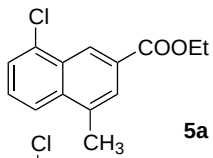
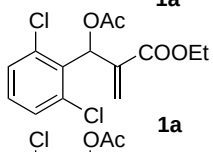
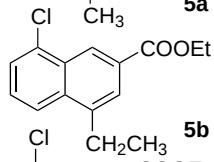
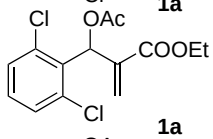
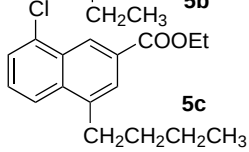
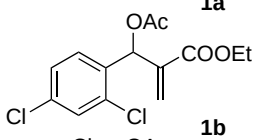
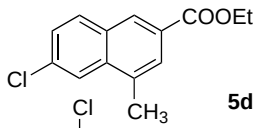
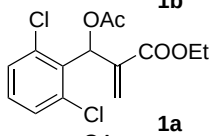
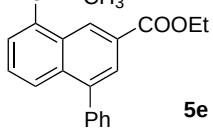
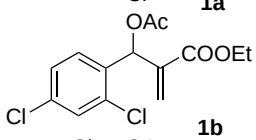
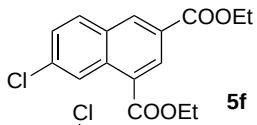
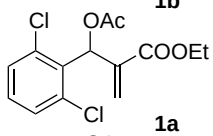
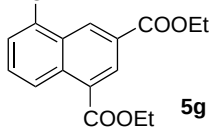
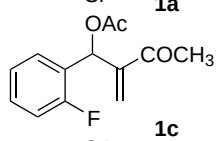
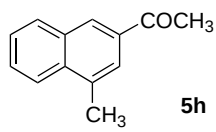
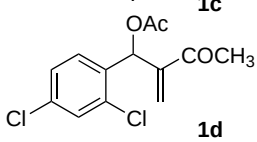
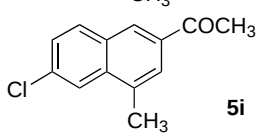
was known,[7] and elimination of nitrous acid can be achieved readily in the presence of base in *N*,*N*-dimethylformamide;[8] thus, we think that the reaction in Scheme 1 would be plausible.

For the conjugate addition of nitroalkane to the Baylis–Hillman acetate, Amri used sodium hydroxide in aqueous tetrahydrofuran.[6] However, ester-containing Baylis–Hillman adducts might cause severe hydrolysis problem under Amri's conditions. For such a reason we investigated the reaction conditions including solvent, base and temperature.[9] The use of potassium carbonate in *N*,*N*-dimethylformamide was found to be the best conditions for the preparation of **3** from the Baylis–Hillman acetates **1**. Moreover, the choice of potassium carbonate in dipolar aprotic solvent, *N*,*N*-dimethylformamide, must be beneficial for the next S_NAr reaction and the elimination of nitrous acid. From the rational design and preliminary search for the reaction conditions, we could prepare some 2-substituted naphthalene derivatives **5** in good yields in a one-pot reaction from the Baylis–Hillman acetates and report herein the preliminary results.

As shown in Table 1, the reaction of Baylis–Hillman acetates **1** and primary nitroalkanes **2** (2 equiv.) in the presence of K_2CO_3 (3 equiv.) in DMF afforded the corresponding naphthalenes **5**. Regardless of the electron withdrawing group on the Baylis–Hillman acetates, ethoxycarbonyl- (entries 1–7) and acetyl- (entries 8–9) naphthalenes **5** were obtained in good yields. When we use the Baylis–Hillman acetate derived from acrylonitrile, the corresponding naphthalene was isolated in trace amounts.[10]

Table 1. Synthesis of naphthalene derivatives **5**

entry	substrate (**1**)	conditions	product (**5**)	yield (%) (mp, °C)
1	 **1a**	$CH_3CH_2NO_2$ (2 equiv) K_2CO_3 (3 equiv) DMF, rt-50 °C, 17 h	 **5a**	75 (52-53)
2	 **1a**	$CH_3CH_2CH_2NO_2$ (2 equiv) K_2CO_3 (3 equiv) DMF, rt-50 °C, 14 h	 **5b**	73 (36-37)
3	 **1a**	$CH_3(CH_2)_3CH_2NO_2$ (2 equiv) K_2CO_3 (3 equiv) DMF, rt-50 °C, 14 h	 **5c**	67 (47-48)
4	 **1b**	$CH_3CH_2NO_2$ (2 equiv) K_2CO_3 (3 equiv) DMF, rt-50 °C, 15 h	 **5d**	68 (79-80)
5	 **1a**	$PhCH_2NO_2$ (2 equiv) K_2CO_3 (3 equiv) DMF, rt-60 °C, 8 h	 **5e**	62 (121-122)
6	 **1b**	O_2NCH_2COOEt (2 equiv) K_2CO_3 (3 equiv) DMF, rt-60 °C, 15 h	 **5f**	79 (87-88)
7	 **1a**	O_2NCH_2COOEt (2 equiv) K_2CO_3 (3 equiv) DMF, rt-60 °C, 6 h	 **5g**	89 (77-78)
8	 **1c**	$CH_3CH_2NO_2$ (2 equiv) K_2CO_3 (3 equiv) DMF, rt-50 °C, 10 h	 **5h**	67 (35-36)
9	 **1d**	$CH_3CH_2NO_2$ (2 equiv) K_2CO_3 (3 equiv) DMF, rt-50 °C, 8 h	 **5i**	60 (92-93)

The reaction mechanism of the reaction is as follows: (1) tandem nucleophilic addition–elimination reaction (S_N2') of **2** to **1** with high stereoselectivity (*E* major)[6,9e] to give **3**; (2) intramolecular S_NAr reaction of **3** gave the dihydronaphthalenes **4**; and finally (3) elimination of nitrous acid to **5**. The assignment of stereochemistry of S_N2' product **3** was based on spectroscopic evidence. The chemical shift trends were consistent with those reported in the literature.[6,9e] The first step, S_N2'-type reaction of nitronate to the Baylis–Hillman acetates, can occur below room temperature in short time. However, the following S_NAr reaction was slow at room temperature. Gentle warming up to ca. 50–60°C quickens the reaction.

The reaction of **1a** and nitroethane is typical: To a stirred solution of well-ground potassium carbonate (414 mg, 3 mmol) in *N*,*N*-dimethylformamide (3 mL) was added nitroethane (150 mg, 2 mmol) at rt and stirred during 10 min. A solution of **1a** (317 mg, 1 mmol) in DMF (1 mL) was added dropwise during 20 min at the same temperature. After stirring for 16 h at 50°C, the reaction mixture was poured into dilute HCl solution. After the usual work-up process, **5a** was isolated by silica gel column chromatography (hexane/CH_2Cl_2, 5:1) as a white solid, 187 mg (75%).[11]

In conclusion, we have disclosed a facile synthetic method of 2-substituted naphthalenes from the Baylis–Hillman acetates. This is the first example of applying the S_NAr concept in the Baylis–Hillman chemistry to form the cyclic compounds to the best of our knowledge. Related application of the tandem S_N2'–S_NAr-elimination chemistry on the Baylis–Hillman adducts are currently underway.

Acknowledgements

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10. The reaction of 3-acetoxy-3-phenyl-2-methylenepropanenitrile, an example of the nitrile-substituted Baylis–Hillman acetate, and nitroethane in the same reaction conditions gave low yield (5%) of corresponding naphthalene, 4-methylnaphthalene-2-carbonitrile. Instead unidentified complex dimeric mixtures and some (ca. 5%) *Z*-form of **3**, which cannot undergo the next S_NAr reaction due to the stereochemical requirement, were obtained.
11. Selected spectroscopic data for **5a**: 187 mg (75%), white solid, mp 52–53°C; IR (KBr) 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (t, $J=7.1$ Hz, 3H), 2.73 (s, 3H), 4.46 (q, $J=7.1$ Hz, 2H), 7.47–7.95 (m, 3H), 7.97 (s, 1H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.04, 20.34, 61.90, 123.89, 126.35, 127.30 (2C from ^1H–^{13}C COSY), 128.34, 128.92, 130.99, 134.62, 135.92, 136.55, 167.29; mass (70 eV) *m*/*z* (rel. intensity) 139 (42), 175 (49), 203 (100), 220 (28), 248 (M^+, 86), 250 (M^++2, 28).