Pergamon

Tetrahedron Letters 42 (2001) 9023–9026

TETRAHEDRON LETTERS

Synthesis of ethyl 3-cyano-2-methylcinnamates and 3-cyano-2-methylcinnamonitriles from the Baylis–Hillman acetates

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Received 29 August 2001; accepted 19 October 2001

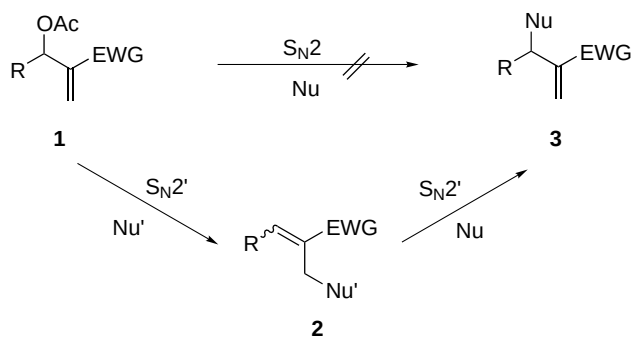
Abstract—The reaction of the DABCO salts **2**, generated in situ from the Baylis–Hillman acetates **1**, and KCN in aqueous THF gave ethyl 3-cyano-2-methylcinnamates **4a–d** and 3-cyano-2-methylcinnamonitriles **4e–f** in good yields.

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

Recently, the Baylis–Hillman adducts and their acetates attracted much attention as synthetic intermediates.[1–3] Various nucleophiles attack the vinyl carbon of the Baylis–Hillman acetates **1** (allylic substitution, S_N2') to give **2**. Direct substitution of nucleophile at the secondary carbon of the Baylis–Hillman acetate (S_N2) leading to **3** has never been reported to the best of our knowledge (Scheme 1). Instead, such substitution can be achieved via the successive S_N2'–S_N2' reaction of the Baylis–Hillman acetates via **2** as shown in Scheme 1.[3,4]

However, the first S_N2' type reaction leading to **2** by the first nucleophile, Nu′, must occur completely in order to synthesize **3** in pure state. Otherwise, the next S_N2' reaction by the second nucleophile, Nu, can occur either at **2** or **1**. In such a situation mixtures might be obtained. Additional requirement for the effective preparation of type **3** compounds is that the first nucleophile should be exchanged by a second nucleophile effectively. In these contexts, transformation of **1** to **2** could be possible with DABCO, DBU or DMAP. However, DABCO is the best choice for the reaction in our case.[5] Some nucleophiles have been used in the second S_N2' step, which include $NaBH_4$,[3a,b] 2-formylimidazole,[3c] zwitterion derived from DABCO and acrylonitrile,[3d] acetate ion[3e,f] and tosylamide.[6]

In the course of our program for the synthesis of pesticidal 2-amino-3-aryl-2-pyrroline derivatives, we needed ethyl 2-methylene-3-cyanohydrocinnamates (type **3**). Thus, we intended to prepare the compounds by the successive S_N2'–S_N2' strategy from the Baylis–Hillman acetates. In this report, we would like to describe the results on the reaction of potassium cya-



Scheme 1.

Keywords: Baylis–Hillman acetates; ethyl 3-cyano-2-methylcinnamates; DABCO.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)01971-2

nide with some DABCO salts of the Baylis–Hillman acetates derived from arylaldehydes. As shown in Scheme 2, the Baylis–Hillman acetates **1a–f** were converted to the DABCO salts **2a–f** in aqueous THF within 15 min quantitatively. Potassium cyanide was added into the in situ generated DABCO salts and the mixture was stirred at room temperature during 30 min. After usual workup and column chromatography, we could obtain ethyl 3-cyano-2-methylcinnamates **4a–d** and 3-cyano-2-methylcinnamonitriles **4e–f** in good yields, unexpectedly, instead of the desired methylene derivatives **3a–f**.[7]

The compounds **4a–f** might be produced by the isomerization of the initially formed methylene derivatives **3a–f**. The E/Z isomer of **4** could be separated nicely ($E/Z = 2/1$–$5/1$) and the results are listed in Table 1. The E-form was the major product, which could be determined by NOE experiments with **4a** and **4e** as the representative examples. Irradiation of the methyl proton ($\delta = 2.10$ ppm) of **4a**-Z showed an increase of aromatic proton, while irradiation of the methyl proton ($\delta = 2.40$ ppm) of **4a**-E did not show any NOE. As shown in Fig. 1 the stereochemistry of **4e**, the nitrile substituted analog, was also determined by NOE experiments. Methyl protons of the E-isomer of **4a–f** appeared in 2.39–2.49 ppm while those of the Z-isomer in 1.92–2.24 ppm.

In contrast, when we used **1g** and **1h**, the Baylis–Hillman acetates derived from *n*-hexanal, somewhat different results were observed. When we used **1g**, expected **4g** was obtained (entry 7). However, in the case of **1h** (entry 8) methylene derivative **3h** was isolated in 73% yield. Isomerization of **3h** into the corresponding **4h** could be carried out at room temperature in the presence of DABCO very slowly.[10] This might be due to the diminished acidity of the proton at the 3-position of **3h**. However, repeated efforts to obtain the methylene derivatives **3a–f**, our initial target compounds, were failed.

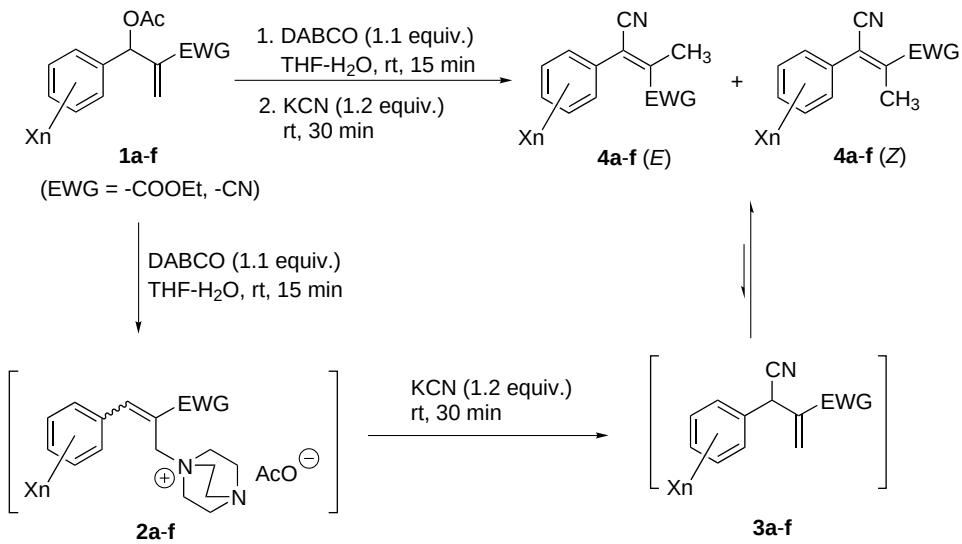
The backbone of **4** could not be found in the literature.[8] The synthesis and applications of ethyl 2-cyano-3-methylcinnamates or 2-cyano-3-methylcinnamonitriles have been reported in many reports,[9] however, 3-cyano derivatives **4** were unknown.

A typical procedure for the synthesis of **4a** is as follows: to a stirred solution of **1a** (248 mg, 1.0 mmol) in aqueous THF (H_2O/THF, 1:3, 4 mL) was added DABCO (123 mg, 1.1 mmol) and stirred at room temperature for 15 min. To the reaction mixture KCN (78 mg, 1.2 mmol) was added and stirred for 30 min. After the usual workup and column chromatography on silica gel (hexane/ether, 3:1) we could obtain analytically pure **4a**-E (160 mg, 74%) and **4a**-Z (30 mg, 14%) as clear oils.

In this report, we disclosed the first synthesis of ethyl 3-cyano-2-methylcinnamates and 3-cyano-2-methylcinnamonitriles by using the successive S_N2'–S_N2'-isomerization strategy with DABCO and KCN from the easily available Baylis–Hillman acetates.

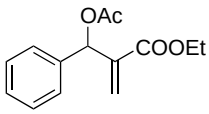
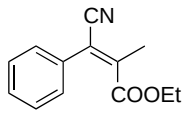
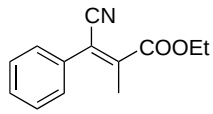
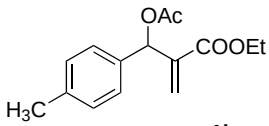
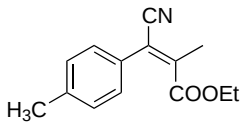
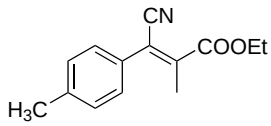
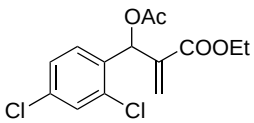
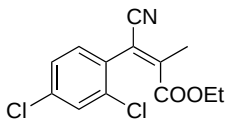
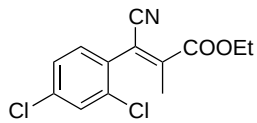
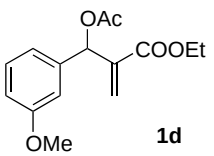
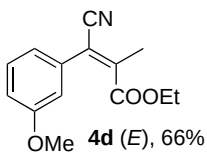
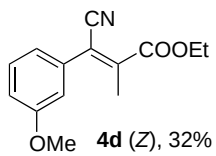
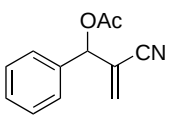
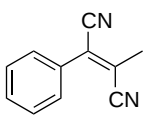
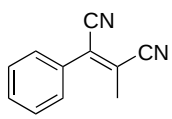
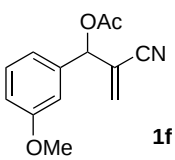
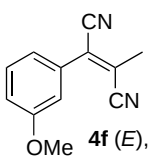
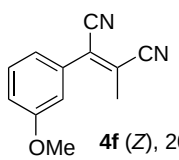
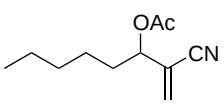
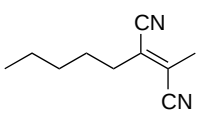
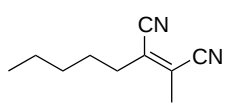
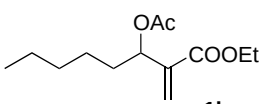
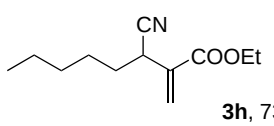
Acknowledgements

This work was supported by Korea Research Foundation Grant (KRF-2001-015-DP0326).



Scheme 2.

Table 1. Synthesis of ethyl 3-cyano-2-methylcinnamates and 3-cyano-2-methylcinnamonitriles

entry	B-H acetates	products (% yield)[a]	
1	 **1a**	 **4a** (*E*), 74%	 **4a** (*Z*),14%
2	 **1b**	 **4b** (*E*), 73%	 **4b** (*Z*), 15%
3	 **1c**	 **4c** (*E*), 72%	 **4c** (*Z*), 19%
4	 **1d**	 **4d** (*E*), 66%	 **4d** (*Z*), 32%
5	 **1e**	 **4e** (*E*), 55%	 **4e** (*Z*), 27%
6	 **1f**	 **4f** (*E*), 41%	 **4f** (*Z*), 20%
7	 **1g**	 **4g** (*E*), 26%	 **4g** (*Z*), 32%
8	 **1h**	 **3h**, 73%[b]	

[a]Isolated yield of pure product. [b]For the isomerization of **3h** to **4h**, see reference 10.

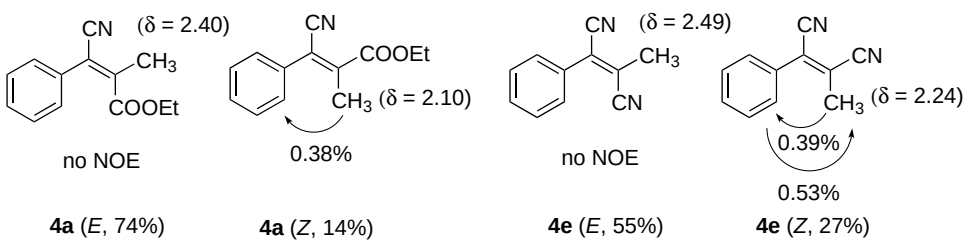


Figure 1.

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3. (a) Basavaiah, D.; Kumaragurubaran, N. *Tetrahedron Lett*. **2001**, *42*, 477; (b) Im, Y. J.; Kim, J. M.; Mun, J. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2001**, *22*, 349; (c) Drewes, S. E.; Horn, M. M.; Ramesar, N. *Synth. Commun*. **2000**, *30*, 1045; (d) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett*. **2001**, *42*, 85; (e) Mason, P. H.; Emslie, N. D. *Tetrahedron* **1994**, *50*, 12001; (f) Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr*. **1989**, 403.
4. The reaction of Baylis–Hillman carbonates and phenols in the presence of palladium catalyst by Trost et al. could be regarded as similar in its basic concept, see: Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc*. **2000**, *122*, 3534. However, in this case the regioselectivity of the reaction is modest (S_N2 type/S_N2' type = 1/2.5–6.7/1).
5. The use of triphenylphosphine instead of DABCO as the first nucleophile gave the reduction products, ethyl 2-methylene-3-phenylpropanoate and ethyl 2-methylcinnamate in low yields. Salt formation with cinchonidine is incomplete.
6. The reaction of *p*-toluenesulfonamide and the DABCO salts of **1** gave the corresponding Baylis–Hillman adducts of *N*-tosylimines. The results will be published soon.
7. Some representative spectroscopic data are as follows: **4a**-*E*: oil; IR (KBr) 2218, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, $J=7.2$ Hz, 3H), 2.40 (s, 3H), 4.05 (q, $J=7.2$ Hz, 2H), 7.33–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.49, 19.45, 60.72, 115.83, 116.69, 126.86, 127.64, 128.38, 132.01, 144.72, 166.34; mass (70 eV) m/z (rel. intensity) 115 (100), 116 (59), 141 (70), 170 (78), 186 (65), 215 (M^+, 86). Anal. calcd for $C_{13}H_{13}NO_2$: C, 75.54; H, 6.09; N, 6.51. Found: C, 75.32; H, 6.15; N, 6.48.
   Compound **4a**-*Z*: oil; IR (KBr) 2216, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (t, $J=7.2$ Hz, 3H), 2.10 (s, 3H), 4.40 (q, $J=7.2$ Hz, 2H), 7.36–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.98, 17.23, 62.33, 117.46, 119.48, 128.88, 128.89, 129.64, 133.41, 143.95, 165.89; mass (70 eV) m/z (rel. intensity) 115 (100), 116 (56), 141 (65), 170 (84), 186 (56), 215 (M^+, 69). Anal. calcd for $C_{13}H_{13}NO_2$: C, 75.54; H, 6.09; N, 6.51. Found: C, 75.50; H, 6.08; N, 6.58.
8. We used STN International and SciFinder Scholar 2000 database in order to confirm the precedence of the compounds.
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10. Isomerization of **3h** into **4h** occurred very slowly. We could obtain **4h** (*E*) and **4h** (*Z*) in 23 and 32% yields, respectively, after 7 days at room temperature in the presence of DABCO (1.0 equiv.).