Synthesis of Ethyl 2-Methylene-3-aryl-4-oxoalkanoates and Ethyl 2-Arylidene-4-oxoalkanoates from the Baylis-Hillman Acetates

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Recently, we are interested in the nucleophilic substitution reaction of the *in situ* generated DABCO (1,4-diazabicyclo-[2.2.2]octane) salt of the Baylis-Hillman acetate.[1] The DABCO salt can be prepared in aqueous THF instantaneously and completely by simply mixing DABCO and the Baylis-Hillman acetate.[1] The reaction of the DABCO salt and nucleophiles such as cyanide,[1a] hydride[1b] and *p*-toluenesulfonamide[1c] occurred in a S_N2' fashion selectively.[1] This two-step reaction can afford a net S_N2 type product from the Baylis-Hillman acetate. Introduction of nucleophiles at the primary position can be carried out by using K_2CO_3 in *N,N*-dimethylformamide (Figure 1).

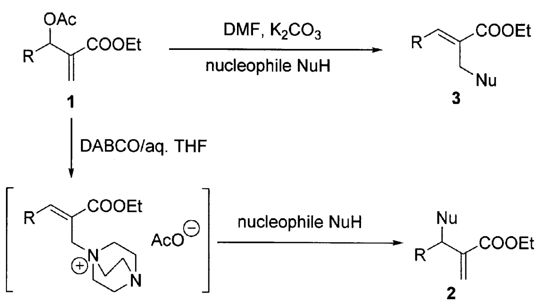
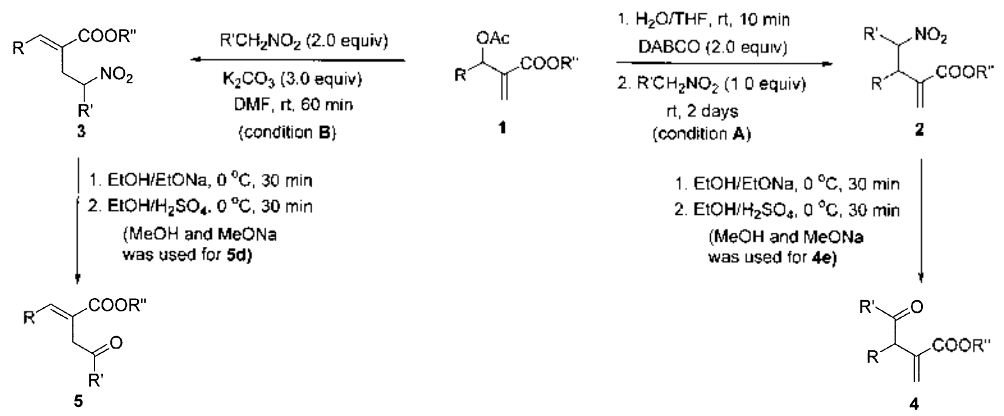


Figure 1

Recently, Amri *et al.* have reported the S_N2' reaction of nitronate anion to the Baylis-Hillman acetate in the presence of NaOH in THF.[2] They obtained 2-alkylidene-4-nitro ketones in moderate yields by using the Baylis-Hillman adducts derived from methyl vinyl ketone and ethyl vinyl ketone. Eventually, they prepared 2-alkylidene-1,4-diketones *via* the Nef reaction.[2] Thus, we intended to examine the reaction of nitronate anion and the Baylis-Hillman acetates derived from ethyl acrylate or methyl acrylate in order to prepare 2-methylene-4-oxoalkanoates or 2-arylidene-4-oxoalkanoates.

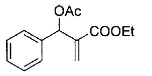
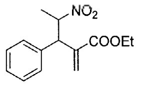
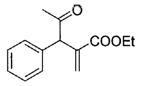
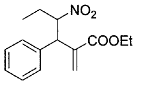
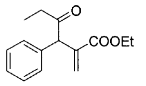
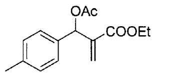
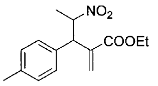
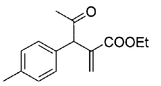
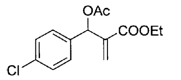
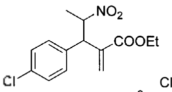
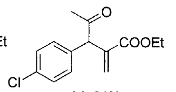
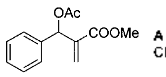
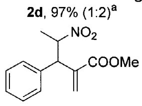
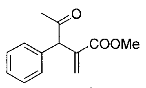
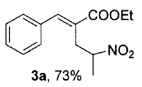
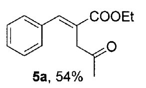
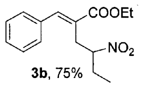
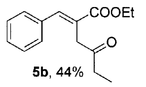
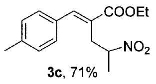
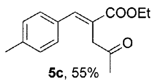
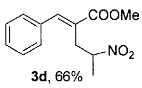
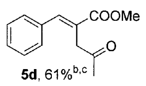
As reported previously the required DABCO salt of the Baylis-Hillman acetate could be prepared *in situ* in aqueous THF at room temperature within 10 min completely.[1] In order to generate simultaneously the nitronate anion and the DABCO salt we used two equivalents of DABCO. Nucleophilic substitution reaction of nitronate anion was then carried out at room temperature for 2 days to give 2-methylene-4-nitroalkanoates **2a-e** in good yields (condition A). As shown in Table 1 (entries 1-5), **2a-e** was obtained as a mixture of diastereomers. The stereochemistry of *syn/anti* was not important in the next Nef reaction. Thus, we did not separate the diastereomers in most cases.[3] In order to prepare 2-arylidene-4-nitroalkanoates **3a-d**, reaction of the Baylis-Hillman acetates **1** and primary nitroalkane was carried out in the presence of potassium carbonate in *N,N*-dimethylformamide (condition B). The stereochemistry of the generated **3a-d** was *E* as previously reported as in other cases.[1,4]

We examined next the possibility of converting 2-methylene-4-nitroalkanoate **2** and 2-arylidene-4-nitroalkanoates **3** into the corresponding ketone derivatives **4** and **5** via the Nef reaction. However, we could not obtain the desired compounds in appreciable amounts with various known methods such as potassium permanganate, cerium ammonium nitrate, or tin chloride.[5] Best results were observed when we used



Scheme 1

Table 1. Synthesis of 2-methylene-4-oxoalkanoates **4** and 2-alkylidene-4-oxoalkanoates **5**

Entry	B-H acetate (1)	Conditions	2 or 3	4 or 5
1	 **1a**	**A** $CH_3CH_2NO_2$	 **2a**, 96% (1:2)[a]	 **4a**, 40%
2	**1a**	**A** $CH_3CH_2CH_2NO_2$	 **2b**, 90% (1.5)[a]	 **4b**, 32%[b]
3	 **1b**	**A** $CH_3CH_2NO_2$	 **2c**, 92% (1:4)[a]	 **4c**, 33%[b]
4	 **1c**	**A** $CH_3CH_2NO_2$	 **2d**, 97% (1:2)[a]	 **4d**, 31%
5	 **1d**	**A** $CH_3CH_2NO_2$	 **2e**, 90% (1:1)[a]	 **4e**, 33%[b,c]
6	**1a**	**B** $CH_3CH_2NO_2$	 **3a**, 73%	 **5a**, 54%
7	**1a**	**B** $CH_3CH_2CH_2NO_2$	 **3b**, 75%	 **5b**, 44%
8	**1b**	**B** $CH_3CH_2NO_2$	 **3c**, 71%	 **5c**, 55%
9	**1d**	**B** $CH_3CH_2NO_2$	 **3d**, 66%	 **5d**, 61%[b,c]

[a]The ratio of *syn*/*anti* was determined in ^1H NMR spectrum (see ref. 3). [b]Trace amounts of 3-alkyl-4-aryl-6*H*-[1,2]oxazine-5-carboxylates were observed. [c]MeOH/MeONa was used.

the following reaction conditions: treatment of **2** and **3** with sodium alkoxide followed by acidic hydrolysis (Amris condition).[2]

Synthesis of ethyl 2-methylene-3-phenyl-4-oxopentanoate (**4a**) is typical: To a stirred solution of the Baylis-Hillman acetate **1a** (496 mg, 2 mmol) in aqueous THF (10 mL, H_2O/THF = 1 : 1) was added DABCO (448 mg, 4 mmol) and stirred at room temperature for 10 min. To this solution was added dropwise the solution of nitroethane (150 mg, 2 mmol) in THF (1 mL) during 10 min and stirred at room temperature for 2 days. After the usual workup process and column chromatographic purification we could obtain the desired compound **2a** in 96% yield (505 mg) as a diastereomeric mixtures (1 : 2).[3,6] To the solution of **2a** (263 mg, 1 mmol) in dry ethanol (2 mL) was added sodium ethoxide solution (340 mg, 1.1 mmol, 21%, Aldrich) and stirred at 0 °C for 30 min. Pouring the reaction mixture into ethanolic sulfuric acid solution at 0 °C and stirred during 30 min. After appropriate workup process and column chromatographic purification (hexane/ether, 20 : 1) we could obtain **4a** in 40% isolated yield (93 mg).[6]

In this communication, we disclosed a facile synthesis of two types of γ-ketoesters. Extension to the γ-ketoalkanenitrile system and the reaction with other nitro compounds including ethyl nitroacetate are understudy.

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References and Notes

1. (a) Chung, Y. M.; Gong, J. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2001**, *42*, 9023. (b) Im, Y. J.; Kim, J. M.; Mun, J. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 349. (c) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, 173.
2. (a) Chamakh, A.; Mhirsi, M.; Villieras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, 295. (b) Hbaieb, S.; Amri, H. *J. Soc. Chim. Tunis.* **2000**, *4*, 671.
3. Assignment of the ratio of *syn*/*anti* was impossible due to similar coupling constant between the two protons at the 3- and 4-position of **2**. As an example, the two isomers of **2a** were separated in 52 and 24%, respectively. Coupling constant *J* of major isomer is 11.2 Hz and 11.6 Hz for minor isomer.[6] In other cases the ratio was determined in their ^1H NMR spectra and used without separation.
4. The stereochemistry of **5a-d** was *E* as that of **3a-d**. During the Nef reaction the stereochemistry was retained. In ^1H NMR spectra, the vinyl peaks appeared at 7.86-8.08 ppm, which was well coincidence with the reported data of similar compounds.[2]
5. Conditions for the Nef reaction, see: (a) Cookson, R. C.; Ray, P. S. *Tetrahedron Lett.* **1982**, *23*, 3521. (b) Das, N. B.; Sarma, J. C.; Sharma, R. P.; Bordoloi, M. *Tetrahedron Lett.* **1993**, *34*, 869. (c) Aizpurua, J. M.; Palomo, O. C. *Tetrahedron Lett.* **1987**, *28*, 5361. (d) Shechter, H.; Williams, F. T. *J. Org. Chem.* **1962**, *27*, 3699. (e) Mcmurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259.
6. Some representative spectroscopic data of **2a**, **4a**, **3d**, and **5d** are as follows.
2a: Major isomer, 52%; R_f = 0.20 (hexane/ether, 8:1); white solid, mp 54-55 °C; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.62 (d, J 6.5 Hz, 3H), 4.17 (q, J 7.2 Hz, 2H), 4.38 (d, J 11.2 Hz, 1H), 5.48 (qd, J 11.2 and 6.5 Hz, 1H), 5.79 (s, 1H), 6.37 (s, 1H), 7.22-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.04, 18.95, 52.22, 61.33, 85.67, 127.27, 127.77, 127.99, 128.71, 137.44, 139.37, 165.76. Minor isomer, 24%; R_f = 0.26 (hexane/ether, 8:1); oil; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3H), 1.40 (d, J = 6.6 Hz, 3H), 4.07-4.16 (m, 2H), 4.46 (d, J 11.6 Hz, 1H), 5.23 (qd, J 11.6 and 6.6 Hz, 1H), 5.90 (s, 1H), 6.35 (s, 1H), 7.24-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.01, 19.15, 51.05, 61.16, 85.11, 124.55, 127.90, 128.77, 128.94, 136.74, 139.66, 165.48.
4a: oil; IR (KBr) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 2.22 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.99 (s, 1H), 5.22 (s, 1H), 6.39 (s, 1H), 7.18-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.13, 29.66, 60.47, 61.17, 127.90, 129.00, 129.09, 129.66, 134.87, 139.91, 166.69, 205.87.
3d: oil; ^1H NMR ($CDCl_3$) δ 1.46 (d, J = 6.7 Hz, 3H), 2.92-3.00 (m, 1H), 3.22-3.30 (m, 1H), 3.85 (s, 3H), 4.86-4.94 (m, 1H), 7.26-7.42 (m, 5H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.76, 32.77, 52.33, 81.66, 127.24, 128.74, 128.79, 128.95, 134.59, 143.53, 167.64.
5d: oil; IR (KBr) 1718, 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 3.62 (s, 2H), 3.80 (s, 3H), 7.26-7.38 (m, 5H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.09, 42.54, 52.25, 126.67, 128.62, 128.76, 128.90, 135.07, 142.26, 167.88, 206.04.