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Applications of Baylis–Hillman acetates: one-pot, facile and convenient synthesis of substituted γ-lactams

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Abstract—A simple, convenient and one-pot transformation of the acetates of Baylis–Hillman adducts into substituted γ-lactams, that is, (*E*)-5-alkyl-3-arylidenepyrrolidin-2-ones via treatment with nitroalkanes in the presence of a base, followed by reductive cyclization, using Fe/AcOH, is described.

The Baylis–Hillman reaction has become a useful synthetic reaction in organic chemistry in recent years because it provides a simple and convenient method for the synthesis of interesting classes of densely functionalized molecules in operationally simple, one-pot, atom economic procedures.[1,2] The γ-lactam framework occupies an important place in nitrogen heterocycles because it is present in various natural products and pharmaceutical agents[3] and hence the development of convenient methods for the synthesis of γ-lactams represents an interesting and attractive endeavor in organic synthesis.[3b,e,k,n,4] In continuation of our interest in the synthesis of heterocyclic molecules,[5] we herein report a facile one-pot synthesis of substituted γ-lactams, that is, (*E*)-5-alkyl-3-arylidenepyrrolidin-2-ones using the acetates of Baylis–Hillman adducts.

Acetates of the Baylis–Hillman adducts have been successfully employed in a number of transformations leading to the synthesis of various important and useful molecules often involving high levels of stereoselectivities.[6] Although there are a number of methods available for the synthesis of γ-lactams,[4] a literature survey revealed no report on the synthesis of 3-arylidene-γ-lactams using acetates of Baylis–Hillman adducts.

The literature also revealed that acetates of the Baylis–Hillman adducts were conveniently transformed into the corresponding (*E*)-2-arylidene-4-nitroalkanoates[6b] [or (*E*)-2-alkylidene-4-nitroalkanoates[6h]] and (*E*)-2-alkylidene-4-nitroalkanones[6g] [via treatment with nitroalkanes in the presence of K_2CO_3/DMF (or NaOH/THF) and NaOH/THF, respectively], which were subsequently converted into γ-keto esters[6b,h] and 1,4-diketones[6g] (Scheme 1).

It occurred to us that reductive cyclization of the (*E*)-2-arylidene-4-nitroalkanoates, which would be obtained in situ via treatment of acetates of Baylis–Hillman adducts with nitroalkanes, with an appropriate reagent could result in the one-pot formation of 5-alkyl-3-arylidenepyrrolidin-2-ones. Accordingly, we first selected methyl 3-acetoxy-3-phenyl-2-methylenepropanoate (**2a**) for reaction with nitroethane (**1a**) in the presence of a base followed by reductive cyclization. The best results were obtained when the ester **2a** (2 mmol) was treated with nitroethane (**1a**) (8 mmol) in the presence of K_2CO_3 (8 mmol) in THF/H_2O at room temperature for 12 h followed by the treatment with Fe/AcOH (after removal of THF and nitroethane under reduced pressure) at reflux temperature for 2 h, providing the product (*E*)-5-methyl-3-benzylidenepyrrolidin-2-one (**3**) in 66% isolated yield after work-up and purification by column chromatography.[7] With a view to examine whether the reaction was more facile and whether the yield of **3** would be higher using a stepwise method, we also isolated the trisubstituted alkene, that is, methyl (*E*)-2-benzylidene-4-nitropentanoate (**3A**). Thus, treatment of the starting material **2a** (2 mmol) with nitroethane (8 mmol) in the presence of K_2CO_3 (8 mmol) in THF (5 mL) and water (0.1 mL) at room temperature for 12 h provided the desired trisubstituted alkene **3A** in 80%

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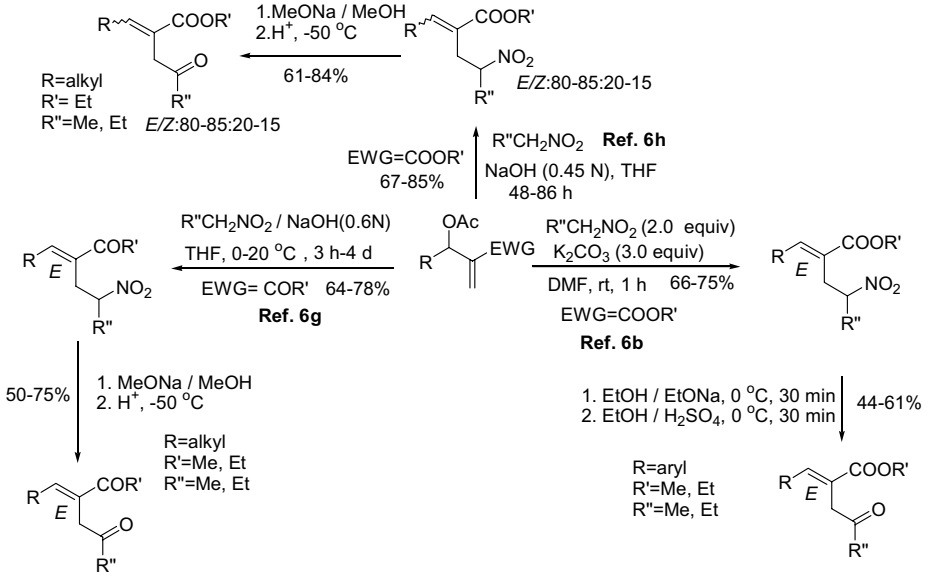
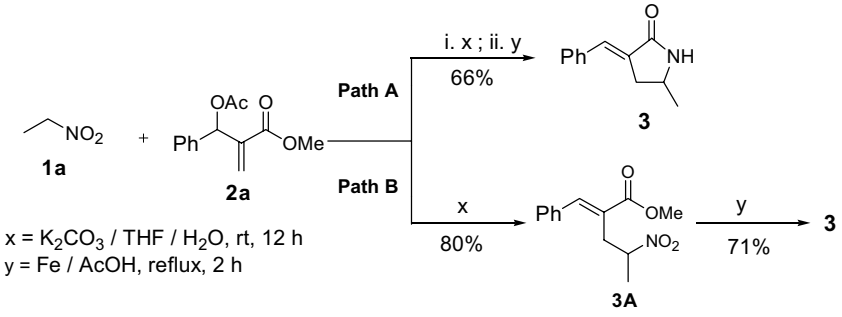
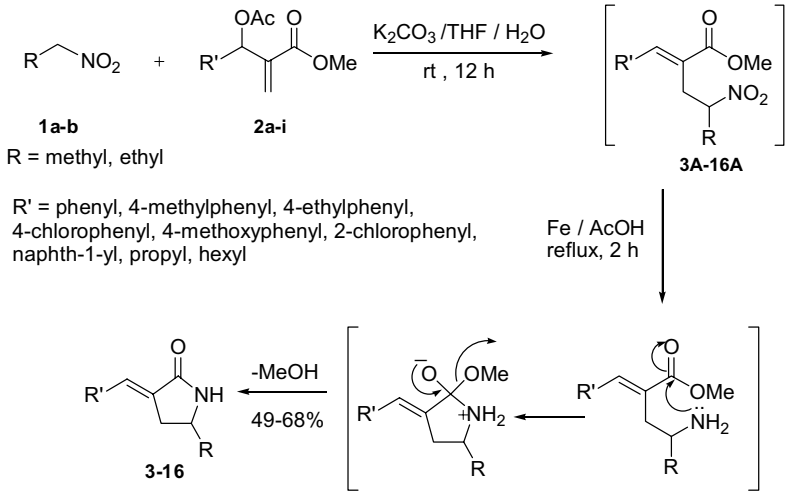


Scheme 1. Synthesis of γ-keto esters and 1,4-diketones using acetates of the Baylis–Hillman adducts.

isolated yield after the usual work-up and column chromatography. The ^{1}H NMR spectrum of the crude product indicated the presence of ≈5% of the *Z*-isomer as was evident from the appearance of a singlet at ca. δ 6.86 (olefinic proton) with a very low intensity. Subsequent treatment of **3A** with Fe/AcOH at 110 °C for 2 h provided the desired γ-lactam **3** in 71% yield (57% overall) (Scheme 2).



Scheme 2. $S_N'2$ reaction of methyl 3-acetoxy-3-phenyl-2-methylenepropanoate (**2a**) with nitroethane (**1a**) followed by reductive cyclization with Fe/AcOH.



Scheme 3. $S_N'2$ reaction on acetates of Baylis–Hillman adducts with nitroalkanes followed by reductive cyclization with Fe/AcOH.

Since the yield was better in the case of the one-pot method we selected the one-pot procedure as the method of choice and extended this strategy to a representative class of the acetates of Baylis–Hillman adducts to provide the desired (*E*)-5-alkyl-3-arylidenepyrrolidin-2-ones **4**–**14** in 55–68% yields (Scheme 3, Table 1). The (*E*)-selectivity of these reactions was established from single crystal X-ray data for pyrrolidinone **11** (Fig. 1).[8]

When we extended this strategy to the acetates **2h**,**i** of Baylis–Hillman adducts derived from butyraldehyde and heptanal, the resulting products, that is, (*E*)-5-methyl-3-butylidenepyrrolidin-2-one **15** and (*E*)-5-methyl-3-heptylidenepyrrolidin-2-one **16** were obtained in 52% and 49% yields, respectively, after column purification. However, the ^{1}H NMR and ^{13}C NMR spectral analysis of the purified products **15** and **16** indicated the presence of ≈8% and ≈10% impurities, respectively. Compound **15** was obtained in pure form after preparative HPLC (Shim pack PREP-ODS column, methanol). However, similar attempts to obtain **16** in chemically pure form were unsuccessful. A plausible mechanism for the one-pot transformation of the acetates of Baylis–Hillman adducts into substituted γ-lactams is presented in Scheme 3.

In conclusion, we have developed a convenient, operationally simple, one-pot procedure for the synthesis of substituted γ-lactams from Baylis–Hillman acetates.

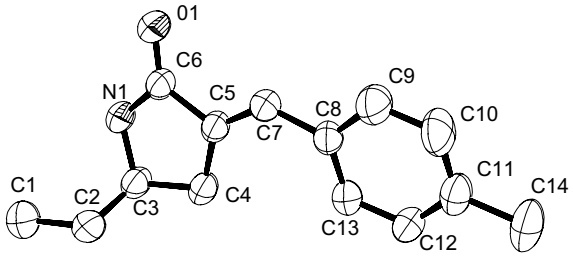


Figure 1. ORTEP diagram of compound **11**.

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Table 1. Synthesis of (*E*)-5-alkyl-3-arylidenepyrrolidin-2-ones[a–f]

Nitroalkane	R	Acetate	R′	Product	Yield (%)	Mp (°C)
1a	Me	**2a**	Phenyl	**3**[g]	66	101–103
1a	Me	**2b**	4-Methylphenyl	**4**	65	170–172
1a	Me	**2c**	4-Ethylphenyl	**5**	68	128–130
1a	Me	**2d**	4-Chlorophenyl	**6**	64	161–163
1a	Me	**2e**	4-Methoxyphenyl	**7**	62	169–171
1a	Me	**2f**	2-Chlorophenyl	**8**	55	124–126
1a	Me	**2g**	Naphth-1-yl	**9**[g]	67	179–181
1b	Et	**2a**	Phenyl	**10**[g]	64	125–127
1b	Et	**2b**	4-Methylphenyl	**11**	62	142–144
1b	Et	**2d**	4-Chlorophenyl	**12**	63	132–134
1b	Et	**2f**	2-Chlorophenyl	**13**	60	128–130
1b	Et	**2g**	Naphth-1-yl	**14**	61	123–125
1a	Me	**2h**	Propyl	**15**[g,h]	52[i]	—
1a	Me	**2i**	Hexyl	**16**[h]	49[i]	—

[a] All reactions were carried out on 2 mmol of the Baylis–Hillman acetate with the nitroalkane (8 mmol), in the presence of K_2CO_3 (8 mmol) in THF/water at room temperature for 12 h and then the reaction mixture was treated with Fe powder (12 mmol)/AcOH (5 mL) (after removal of THF and nitroalkane under reduced pressure) at 110 °C for 2 h.

[b] The compounds **3**–**14** were obtained as solids while compounds **15** and **16** were obtained as viscous liquids. All the compounds **3**–**15** were characterized by IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) spectral data and elemental analyses.

[c] The (*E*)-stereochemistry of compound **11** was established by single crystal X-ray data and the stereochemistry of the other compounds was assigned in analogy to **11**.

[d] Yields are of the pure products (based on acetates) after purification via silica gel column chromatography.

[e] In the case of molecules **6**, **10**, **12**–**14**, the ^{1}H NMR spectra of the crude products showed ≈5–10% of uncyclized compound as evidenced by the singlet at ≈δ 7.81–8.30 (olefinic proton) and the singlet at ≈δ 3.85–3.92 ($COOCH_3$) with low intensity.

[f] The ^{1}H NMR spectra of the crude products did not indicate clearly the presence of any isomeric impurity [on the basis of the ^{1}H NMR spectrum of the crude product **3A** (uncyclized product), which showed the presence of ≈5% (*Z*)-isomeric impurity; we believe that all these reactions are at least ≈95% (*E*)-selective].

[g] Structures were further confirmed by mass spectral analyses.

[h] The ^{1}H NMR spectra of the crude nitro compounds **15A** and **16A** derived from aliphatic acetates **2h** and **2i** indicated the presence of ≈11% and 13% (*Z*)-isomers as evidenced by the triplet at ≈δ 6.05 (olefinic proton *trans* to the ester group).

[i] ^{1}H NMR and ^{13}C NMR spectral analysis of the column purified products **15** and **16** indicated the presence of ≈8% and ≈10% impurities, respectively. However, compound **15** was obtained in pure form after preparative HPLC (Shim pack PREP-ODS column, methanol).

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7. Typical experimental procedure: (*E*)-5-Methyl-3-benzylidenepyrrolidin-2-one **3**: To a stirred mixture of nitroethane (8 mmol, 0.6 g) and K_2CO_3 (8 mmol, 1.104 g) in THF (5 mL) and water (0.1 mL), was added methyl 3-acetoxy-3-phenyl-2-methylenepropanoate (**2a**) (2 mmol, 0.468 g) at room temperature. After stirring at room temperature for 12 h, THF and nitroethane were removed under reduced pressure. The reaction mixture was diluted with acetic acid (5 mL) and Fe powder (12 mmol, 0.67 g) was added. The reaction mixture was heated under reflux (at 110 °C) for 2 h and then was allowed to cool to room temperature. Acetic acid was removed under reduced pressure and the reaction mixture was diluted with EtOAc (10 mL), stirred for 2 min and filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (10 mL). The filtrate and washings were combined and dried over anhydrous

Na_2SO_4. The solvent (EtOAc) was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel) using 70% EtOAc in hexanes to afford (*E*)-5-methyl-3-benzylidenepyrrolidin-2-one (**3**) as a light yellow solid in 66% yield (0.247 g). Mp: 101–103 °C; IR (KBr): 3200–2800 (multiple bands), 1685, 1647 cm^{-1}; ^1H NMR: δ 1.32 (d, 3H, $J = 6.0$ Hz), 2.58–2.77 (m, 1H), 3.32 (ddd, 1H, $J = 2.6$, 7.8, 17.6 Hz), 3.82–4.03 (m, 1H), 7.04 (br, 1H), 7.28–7.54 (m, 6H); ^{13}C NMR: δ 23.26, 34.95, 47.52, 128.35, 128.54, 129.41, 130.12, 131.33, 135.73, 172.05; EIMS: 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.85; H, 7.03; N, 7.52.

8. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **11** CCDC #217594). Crystal data for **11**: empirical formula, $C_{14}H_{17}NO$; formula weight, 215.29; crystal colour, habit: light yellow, rectangular; crystal dimensions, $0.64 \times 0.55 \times 0.48$ mm; crystal system, monoclinic; lattice type, primitive; lattice parameters, $a = 10.048(4)$ Å, $b = 11.595(5)$ Å, $c = 11.158(3)$ Å; $\beta = 112.97(3)$; $V = 1196.9(8)$ $Å^3$; space group, $P2_1/a$ (no. 14); $Z = 4$; $D_{calcd} = 1.195$ g/cm^3; $F_{000} = 464$; $\lambda(MoK_\alpha) = 0.71073$ Å; $R(I \geqslant 3\sigma_1) = 0.0660$, $wR^2 = 0.1914$.