

A Facile Synthesis of 4-Arylidene-2-substituted Isoxazolidin-5-ones from Baylis-Hillman Acetates

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Recently, we have reported the regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles from Baylis-Hillman adducts.¹ In the reaction some hydrazine hydrochlorides gave the pyrazoles in excellent yields in dichloroethane at reflux temperature.¹ As a continuing effort to prepare useful heterocyclic compounds from Baylis-Hillman adducts, we envisioned that we could prepare *N*-substituted isoxazolidin-5-ones from the reaction of *N*-alkylhydroxylamines and Baylis-Hillman adducts.

The addition reaction of *N*-substituted hydroxylamines to α,β -unsaturated esters is a general procedure for the synthesis of isoxazolidin-5-one derivatives.²⁻⁵ The reaction of *N*-alkylhydroxylamines and conjugated esters,^{3a-c,4b} lactones,^{3d,3e} or lactams^{3f} has been employed in the synthesis of isoxazolidinyl nucleosides,^{3b,1b} carbapenems,^{3d} and β -amino acids.^{3g,5a}

As an initial trial, we examined the reaction of Baylis-Hillman adduct with *N*-methylhydroxylamine hydrochloride in DMF in the presence of Et₃N. We obtained the addition product in 73% yield. However, the next conversion into the desired *N*-methyl isoxazolidinone **4a** failed. As a next trial, we examined the reaction of the Baylis-Hillman acetate **1a** with *N*-methylhydroxylamine hydrochloride (**2a**) in DMF in the presence of Et₃N and we obtained the S_N2' type product **3a** in 60% yield. With this compound in our hand we examined the subsequent cyclization under various reaction conditions.⁶ Among them the conditions using LiClO₄ in CH₃CN at reflux temperature afforded the desired compound **4a** in quantitative yield.⁷ In this communication we wish to report the results.

As shown in Scheme 1 and in Table 1, the S_N2' type compounds **3a-g** were synthesized in 51-88% yields within

3 h. The next cyclization step proceeded in quantitative yields in most cases. The reaction with **3e**, containing furanyl group, provided many by-products, presumably due to the Lewis basic nature of the furan moiety. Running the reaction even at room temperature could not completely prevent the formation of by-products, furnished the desired compound in 53% yield (entry 5).

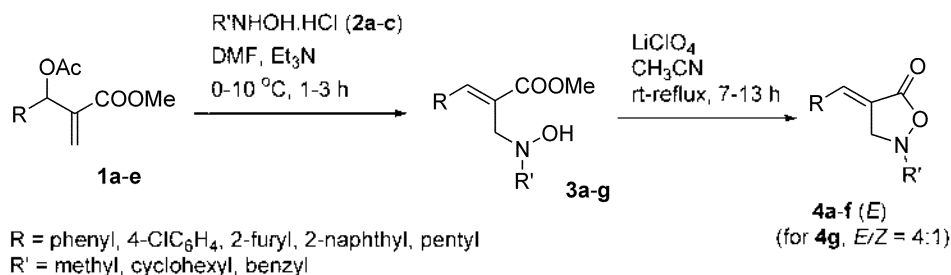
The stereochemistry of the arylidene part is tentatively assigned to be *E*. This trend is general in the S_N2' type reaction of nucleophiles and Baylis-Hillman acetates derived from methyl acrylate as was reported previously.⁸ It is noteworthy that the alkyl-substituted Baylis-Hillman acetate **1e** provided a mixture of *E* and *Z* in a ratio of 4 to 1,⁷ the reason of which is not clear at the moment.

In summary, we have developed a facile synthetic method of synthetically useful 4-arylidene-2-substituted isoxazolidin-5-one derivatives in excellent yields.

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References and Notes

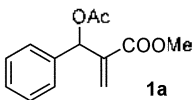
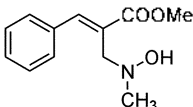
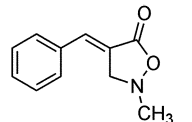
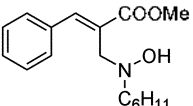
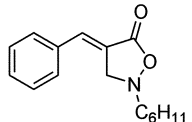
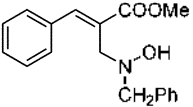
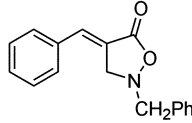
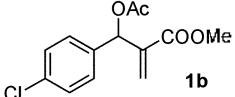
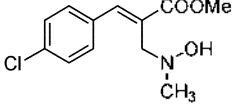
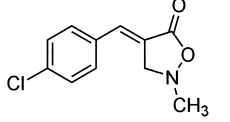
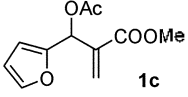
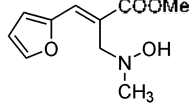
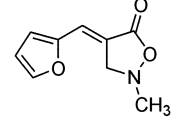
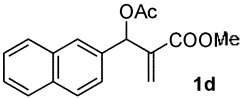
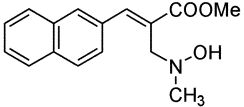
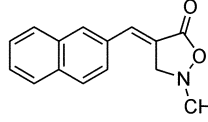
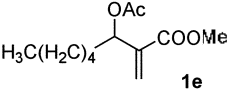
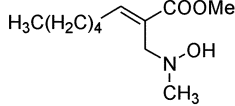
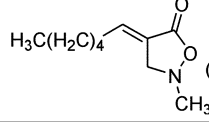
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Scheme 1

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Table 1. Synthesis of 4-arylidene-2-substituted isoxazolidin-5-ones **4**

Entry	B-H acetate 1	Conditions	S _N 2' product 3	Yields (%)	Conditions	Isoxazolidinone 4	Yields (%)
1		CH ₃ NHOH.HCl (2a , 1 equiv.) Et ₃ N (1.1 equiv.) DMF, 0-10 °C, 2 h		3a (60)	LiClO ₄ (1 equiv.) CH ₃ CN reflux, 11 h		4a (100)
2	1a	C ₆ H ₁₁ NHOH.HCl (2b , 1 equiv.) Et ₃ N (1.1 equiv.) DMF, 0-10 °C, 2 h		3b (76)	LiClO ₄ (1 equiv.) CH ₃ CN reflux, 7 h		4b (99)
3	1a	BnNHOH.HCl (2c , 1 equiv.) Et ₃ N (1.1 equiv.) DMF, 0-10 °C, 2 h		3c (61)	LiClO ₄ (1 equiv.) CH ₃ CN reflux, 8 h		4c (99)
4		2a (1 equiv.) Et ₃ N (1.1 equiv.) DMF, 0-10 °C, 2 h		3d (88)	LiClO ₄ (1 equiv.) CH ₃ CN reflux, 9 h		4d (97)
5		2a (1 equiv.) Et ₃ N (1.1 equiv.) DMF, 0-10 °C, 1 h		3e (61)	LiClO ₄ (1 equiv.) CH ₃ CN rt, 12 h		4e (53)
6		2a (1 equiv.) Et ₃ N (1.1 equiv.) DMF, 0-10 °C, 3 h		3f (66)	LiClO ₄ (1 equiv.) CH ₃ CN reflux, 12 h		4f (100)
7		2a (1 equiv.) Et ₃ N (1.1 equiv.) DMF, 0-10 °C, 2 h		3g (51)	LiClO ₄ (1 equiv.) CH ₃ CN rt, 13 h		4g (82, E+Z)

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6. The cyclization of **3a** is not effective in the presence of *p*-TsOH or acetic acid in benzene or in toluene.
7. Typical experimental procedures for the synthesis of **3a** and **4a**: To a stirred mixture of the Baylis-Hillman acetate **1a** (468 mg, 2 mmol) and *N*-methylhydroxylamine hydrochloride (**2a**, 168 mg, 2 mmol) in DMF (5 mL) was added Et₃N (222 mg, 2.2 mmol) at 0-10 °C and stirred at the temperature for 2 h. After usual aqueous workup and column chromatographic purification process (hexanes/ether, 3 : 1) we obtained **3a** (265 mg, 60%). To a stirred

solution of **3a** (221 mg, 1 mmol) in CH₃CN (5 mL) was added LiClO₄ (106 mg, 1 mmol) and heated to reflux for 11 h. After usual aqueous workup and column chromatographic purification process (hexanes/ether, 4 : 1) we obtained **4a** (189 mg, 100%) as a white solid. Other compounds were synthesized similarly.

- The spectroscopic data of **3a**, **4a**, and **4g** are as follows. **3a**: clear oil; ¹H NMR (CDCl₃) δ 2.68 (s, 3H), 3.74 (s, 2H), 3.78 (s, 3H), 7.31-7.51 (m, 3H), 7.57-7.63 (m, 2H), 7.83 (s, 1H). **4a**: white solid, mp 88-89 °C; ¹H NMR (CDCl₃) δ 2.96 (s, 3H), 4.00 (br s, 1H), 4.75 (br s, 1H), 7.37-7.51 (m, 5H), 7.58 (t, *J* = 3.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 48.64, 60.06, 123.61, 129.07, 129.87, 130.35, 133.87, 137.33, 170.43. **4g** (*Z*): ¹H NMR (CDCl₃) δ 0.86-0.93 (m, 3H), 1.25-1.36 (m, 4H), 1.43-1.56 (m, 2H), 2.21-2.22 (m, 2H), 2.91 (s, 3H), 3.63 (br s, 1H), 4.38 (br s, 1H), 6.72-6.80 (m, 1H); ¹³C NMR (CDCl₃) δ 13.86, 22.33, 27.69, 30.43, 31.33, 48.41, 58.51, 125.70, 141.60, 169.28. **4g** (*E*): ¹H NMR (CDCl₃) δ 0.86-0.93 (m, 3H), 1.25-1.36 (m, 4H), 1.43-1.56 (m, 2H), 2.65-2.75 (m, 2H), 2.88 (s, 3H), 3.63 (br s, 1H), 4.38 (br s, 1H), 6.25-6.32 (m, 1H); ¹³C NMR (CDCl₃) δ 13.90, 22.36, 27.33, 28.51, 31.29, 47.79, 61.91, 123.92, 144.60, 168.41.
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