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,4b] 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 Et_3N. 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 Et_3N 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 $LiClO_4$ in CH_3CN 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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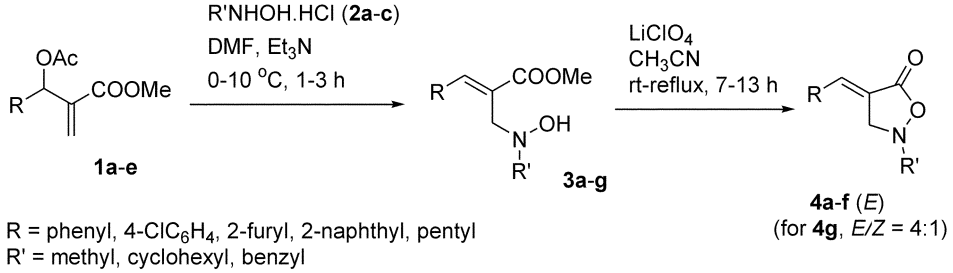

Scheme 1

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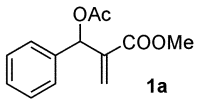
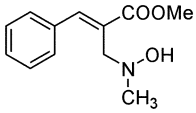
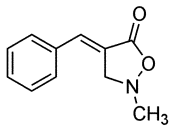
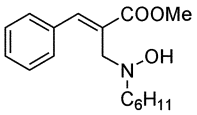
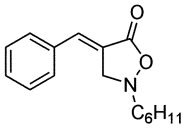
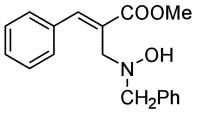
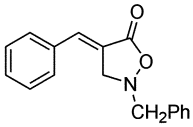
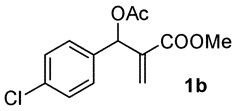
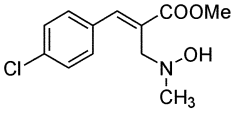
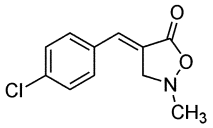
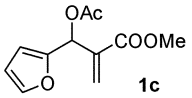
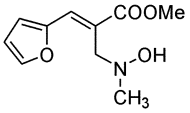
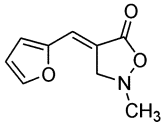
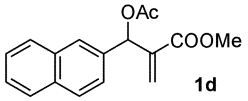
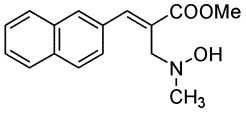
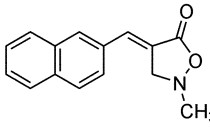
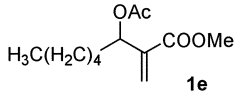
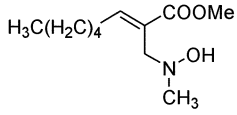
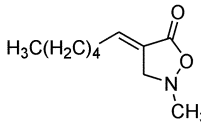
Table 1. Synthesis of 4-arylidene-2-substituted isoxazolidin-5-ones **4**

Entry	B-H acetate **1**	Conditions	S_N2' product **3**	Yields (%)	Conditions	Isozazolidinone **4**	Yields (%)
1	 **1a**	$CH_3NHOH.HCl$ (**2a**, 1 equiv.) Et_3N (1.1 equiv.) DMF, 0-10 °C, 2 h		**3a** (60)	$LiClO_4$ (1 equiv.) CH_3CN reflux, 11 h		**4a** (100)
2	**1a**	$C_6H_{11}NHOH.HCl$ (**2b**, 1 equiv.) Et_3N (1.1 equiv.) DMF, 0-10 °C, 2 h		**3b** (76)	$LiClO_4$ (1 equiv.) CH_3CN reflux, 7 h		**4b** (99)
3	**1a**	BnNHOH.HCl (**2c**, 1 equiv.) Et_3N (1.1 equiv.) DMF, 0-10 °C, 2 h		**3c** (61)	$LiClO_4$ (1 equiv.) CH_3CN reflux, 8 h		**4c** (99)
4	 **1b**	**2a** (1 equiv.) Et_3N (1.1 equiv.) DMF, 0-10 °C, 2 h		**3d** (88)	$LiClO_4$ (1 equiv.) CH_3CN reflux, 9 h		**4d** (97)
5	 **1c**	**2a** (1 equiv.) Et_3N (1.1 equiv.) DMF, 0-10 °C, 1 h		**3e** (61)	$LiClO_4$ (1 equiv.) CH_3CN rt, 12 h		**4e** (53)
6	 **1d**	**2a** (1 equiv.) Et_3N (1.1 equiv.) DMF, 0-10 °C, 3 h		**3f** (66)	$LiClO_4$ (1 equiv.) CH_3CN reflux, 12 h		**4f** (100)
7	 **1e**	**2a** (1 equiv.) Et_3N (1.1 equiv.) DMF, 0-10 °C, 2 h		**3g** (51)	$LiClO_4$ (1 equiv.) CH_3CN 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 Et_3N (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 CH_3CN (5 mL) was added $LiClO_4$ (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; ^{1}H NMR ($CDCl_3$) 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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 48.64, 60.06, 123.61, 129.07, 129.87, 130.35, 133.87, 137.33, 170.43. **4g** (*E*): ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 13.86, 22.33, 27.69, 30.43, 31.33, 48.41, 58.51, 125.70, 141.60, 169.28. **4g** (*Z*): ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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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