

γ -Regioselectivity of (furan-2-yloxy)-trimethyl-silane towards iminium salts: synthesis of γ -arylidenebutenolides

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Abstract

The aminoalkylation of (furan-2-yloxy)trimethylsilane (**1**) from inexpensive starting materials yields γ -butenolides **4**. Preformed and *in situ* generated ternary iminium salts are used. In contrast to other methodologies, no mercury or silver catalysts are necessary for this procedure.

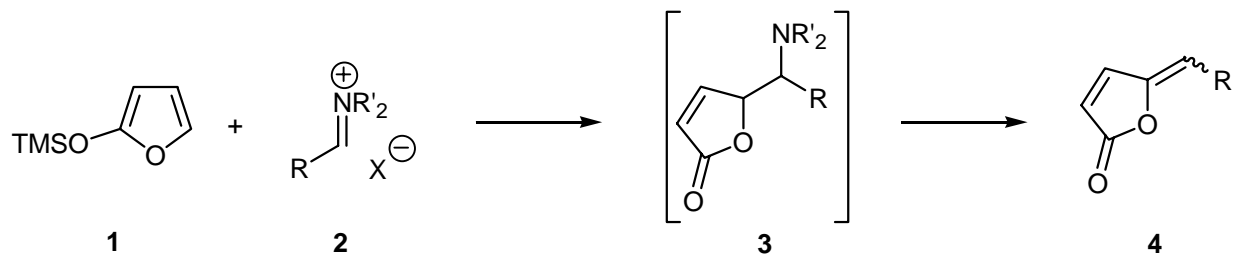
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Introduction

The aminoalkylation of carbonyl compounds with ternary iminium salts is of general interest.¹⁻⁹ Recently, we have disclosed that the aminoalkylation of ketones, enamines, imines (derivatives of aldehydes, cyclic or acyclic ketones), and aromatic compounds provides the corresponding Mannich bases in excellent yields and diastereoselectivities.^{1,2,8-11} By contrast, only a few other types of nucleophiles have been treated with ternary iminium salts containing aryl and carboxylate groups, presumably of the difficult preparation and handling of these compounds.¹²⁻¹⁴ (Furan-2-yloxy)trimethylsilane (**1**) and related structures play an important role for vinylogous aldol-type and Mannich-type reactions.^{15,16} Reactions of **1** with imine-Lewis acid complexes, O-silylated nitrones and cyclic heteroatom-stabilized carbenium ions have already been described.¹⁶

Results and Discussion

This paper describes the reaction of (furan-2-yloxy)trimethylsilane (**1**) with preformed (R = Ph, X = Cl, method A) and *in situ* generated iminium salts **2** (R = CO₂Et, X = Bt,¹⁷ method B) (Scheme 1). The results are shown in Table 1.



2, 3, 4	R	R'	R'	X
a	Ph	Me	Me	Cl
b	4-MePh	Me	Me	Cl
c	4-MeOPh	Me	Me	Cl
d	4-BrPh	-(CH ₂) ₂ O(CH ₂) ₂ -		Cl
e	CO ₂ Et	Me	Me	Bt ¹⁷

Scheme 1

Table 1. Aminoalkylation of (furan-2-yloxy)trimethylsilane (**1**) with ternary iminium salts **2**

Entry	Iminium salt	Method ^a	R	R'	R'	X	Product	Yield ^b (%)	Ratio ^c (Z/E)
1	2a	A	Ph	Me	Me	Cl	4a	91	66:34
2	2b	A	4-MePh	Me	Me	Cl	4b	75	78:22
3	2c	A	4-MeOPh	Me	Me	Cl	4c	67	80:20
4	2d	A	4-BrPh	-(CH ₂) ₂ O(CH ₂) ₂ -		Cl	4d	72	83:17
5	2e	B	CO ₂ Et	Me	Me	Bt ¹⁷	4e	83	77:23

^a see experimental section. ^b isolated yields. ^c determined by ¹H NMR.

Reaction with the preformed iminium salts **2a-d** does not provide the aminoalkylated products **3**. The δ-aminobutenolides **3** formed as intermediates undergo spontaneous deamination to produce the γ-arylidenebutenolides **4a-d** (Table 1, Entries 1-4). Butenolides are an important class of organic compounds existing in natural products and related compounds, which exhibit various interesting biological activities.¹⁸⁻²³ Even though the reaction is carried out under the mildest conditions possible (-40 °C, 2 h),⁸⁻¹⁰ the formation of a delocalized π-electron system is the motivation for the amine elimination. The use of iminium salt **2e** generated *in situ* proceeding

from ethyl benzotriazol-1-yl-dimethylaminoacetate²⁴ shows the same result producing the γ -acetic acid ethyl ester butenolide **4e** (Table 1, Entry 5).

This reaction produces mixtures of two compounds in good yields, which are separated by column chromatography, affording the *Z*-isomers as a major product and the *E*-isomers. Assignment of the geometrical configuration to each of the two lactones can be made by the ¹H NMR spectral data on the basis of chemical shifts of exocyclic olefinic protons. Chemical shifts at lower fields are assigned to the *E*-isomers due to the deshielding effect of the lactone oxygen for the *E*-isomers. The differences of the chemical shift values for the isomers are about 0.75 ppm. For products **4a**, **4c** and **4e** these considerations can be proven by comparison of the ¹H and ¹³C NMR spectral data with authentic samples described in the literature.^{18, 23-26}

Our methodology of preparing γ -arylidenebutenolides **4a-d** has a notable advantage compared to literature. By using the preformed iminium salts, no catalysts are necessary to produce the products in good yields. Other methodologies described in the literature make use of mercury, silver or palladium-catalysts for cyclisation of (*Z*)-2-alken-4-ynoic acids or coupling of (*Z*)- β -halo acrylic acids with arylethyne.^{18, 22-26}

In summary, the diversity in the chemistry of Mannich-type reactions is extended by the use of ternary iminium salts for the reaction with silyloxy dienes. As far as we know, this is the first vinylogous Mannich reaction employing preformed ternary iminium salts. This method affords a simple synthesis of butenolides employing inexpensive and readily available chemicals. We are currently investigating the application of the methodology to make use of the δ -amino-butenolides **3** formed as intermediates.

Experimental Section

General Procedures. All solvents were dried by standard methods prior to use. Column chromatography was performed on silica gel (Macherey-Nagel 60, 0.063-0.200 mm). Melting points were determined by a Büchi SMP-20 melting point apparatus and are uncorrected. IR spectra were measured on a Nicolet 510 P FT-IR spectrometer. GC/MS data were obtained from a Finnigan MAT Magnum TM. ¹H and ¹³C NMR spectra were recorded on a Bruker ARX200 FT-NMR spectrometer (200 MHz for ¹H and 50 MHz for ¹³C). Chemical shifts (δ in ppm) are given from internal TMS.

Method A

All reactions were conducted under argon. A solution of (furan-2-yloxy)trimethylsilane (**1**) (0.25 mL, 1.5 mmol) in anhyd MeCN (10mL) was cooled to 0 °C and the preformed iminium salt **2**^{8,12,28} (1.5 mmol) was added in one portion under stirring. After a reaction time of 2 h at this temperature, the reaction mixture was heated under reflux for additional 2 h. Afterwards the mixture was quenched with aq HCl (37% HCl-H₂O, 1:1, 5 mL) and stirred for 10 min. The

product was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers were dried with Na₂SO₄. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (CH₂Cl₂, CH₂Cl₂-MeOH, 95:5).

5-Benzylidene-5H-furan-2-one (4a). Starting material: (**2a**) (120 mg, 0.7 mmol). m.p.: 85 °C (yellow solid). Lit.¹⁸ m.p.: 86-87 °C. **IR** (KBr): $\tilde{\nu}$ [cm⁻¹] = 3444, 3055, 2987, 1635, 1421, 1265, 896, 744, 705; **GC/MS** (80 eV): m/z (%) = 172 ([M]⁺, 100), 144 (8), 115 (18), 89 (10), 63 (5); **Z-4a**: ¹H NMR (CDCl₃): δ = 6.06 (s, 1 H, OC=CH), 6.23 (d, 1 H, J = 5.3 Hz, COCH=CH), 7.34-7.48 (m, 3 H, Ar-H), 7.53 (d, 1 H, J = 5.3 Hz, COCH=CH), 7.76-7.86 (m, 2 H, Ar-H); ¹³C NMR (CDCl₃): δ = 114.72 (d, OC=CH), 118.51 (d, COCH=CH), 129.28, 129.76, 131.18 (d, CH_{arom}), 133.26 (s, C_{arom}), 145.80 (d, COCH=CH), 148.85 (s, OC=CH), 170.68 (s, C=O); **E-4a**: ¹H NMR (CDCl₃): δ = 6.37 (dd, 1 H, J = 5.6 Hz, J = 1.8 Hz, COCH=CH), 6.84 (s, 1 H, OC=CH), 7.34-7.51 (m, 6 H, COCH=CH, Ar-H); ¹³C NMR (CDCl₃): δ = 116.39 (d, OC=CH), 122.21 (d, COCH=CH), 129.48, 129.60, 131.18 (d, CH_{arom}), 133.38 (s, C_{arom}), 141.15 (d, COCH=CH), 150.65 (s, OC=CH), 169.69 (s, C=O).

5-(4-Methylbenzylidene)-5H-furan-2-one (4b). Starting material (**2b**) (260 mg, 1.5 mmol). m.p.: 81 °C (yellow solid). **IR** (KBr): $\tilde{\nu}$ [cm⁻¹] = 3055, 2987, 1763, 1421, 1265, 894, 741, 706; **GC/MS** (80 eV): m/z (%) = 186 ([M]⁺, 100), 170 (11), 156 (6), 128 (5), 115 (13), 105 (4), 89 (2), 63 (3); **Z-4b**: ¹H NMR (CDCl₃): δ = 2.39 (s, 3 H, CH₃), 6.03 (s, 1 H, OC=CH), 6.20 (d, 1 H, J = 5.3 Hz, COCH=CH), 7.23 (d, 2 H, J = 8.1 Hz, Ar-H), 7.51 (d, 1 H, J = 5.3 Hz, COCH=CH), 7.71 (d, 2 H, J = 8.1 Hz, Ar-H); ¹³C NMR (CDCl₃): δ = 21.93 (q, CH₃), 114.98 (d, OC=CH), 117.94 (d, COCH=CH), 130.06 (d, CH_{arom}), 130.53 (s, C_{arom}), 131.21 (d, CH_{arom}), 140.23 (s, C_{arom}), 145.82 (d, COCH=CH), 148.32 (s, OC=CH), 170.93 (s, C=O); **E-4b**: ¹H NMR (CDCl₃): δ = 2.42 (s, 3 H, CH₃), 6.36 (d, 1 H, J = 5.5 Hz, COCH=CH), 6.81 (s, 1 H, OC=CH), 7.21-7.35 (m, 4 H, Ar-H), 7.86 (d, 1 H, J = 5.5 Hz, COCH=CH); ¹³C NMR (CDCl₃): δ = 21.75 (q, CH₃), 116.60 (d, OC=CH), 121.73 (d, COCH=CH), 129.55, 130.23 (d, CH_{arom}), 130.51, 139.62 (s, C_{arom}), 141.09 (d, COCH=CH), 150.19 (s, OC=CH), 169.83 (s, C=O).

5-(4-Methoxybenzylidene)-5H-furan-2-one (4c). Starting material (**2c**) (300 mg, 1.5 mmol). m.p.: 109 °C (yellow-brown solid). Lit.²⁵ m.p.: 107-110 °C. **IR** (KBr): $\tilde{\nu}$ [cm⁻¹] = 3448, 3055, 1759, 1604, 1421, 1265, 895, 741, 706; **GC/MS** (80 eV): m/z (%) = 202 ([M]⁺, 100), 173 (5), 156 (2), 130 (9), 115 (4), 103 (14), 91 (6), 63 (2); **Z-4c**: ¹H NMR (CDCl₃): δ = 3.84 (s, 3 H, OCH₃), 6.00 (s, 1 H, OC=CH), 6.15 (d, 1 H, J = 5.3 Hz, COCH=CH), 6.92 (d, 2 H, J = 8.9 Hz, Ar-H), 7.48 (d, 1 H, J = 5.3 Hz, COCH=CH), 7.76 (d, 2 H, J = 8.9 Hz, Ar-H); ¹³C NMR (CDCl₃): δ = 55.76 (q, OCH₃), 114.76 (d, OC=CH), 114.81 (d, CH_{arom}), 117.19 (d, COCH=CH), 126.12 (s, C_{arom}), 132.94 (d, CH_{arom}), 145.71 (d, COCH=CH), 147.49 (s, OC=CH), 160.94 (s, Ar-OMe), 171.06 (s, C=O); **E-4c**: ¹H NMR (CDCl₃): δ = 3.86 (s, 3 H, CH₃), 6.28-6.36 (m, 1 H, COCH=CH), 6.75 (s, 1 H, OC=CH), 6.88-7.01 (m, 2 H, Ar-H), 7.28-7.39 (m, 1 H, COCH=CH), 7.71-7.88 (m, 2 H, Ar-H); ¹³C NMR (CDCl₃): δ = 55.82 (q, CH₃), 115.05 (d, CH_{arom}), 116.47 (d,

OC=CH), 121.38 (d, COCH=CH), 125.82 (s, C_{arom}), 131.273 (d, CH_{arom}), 140.94 (d, COCH=CH), 149.48 (s, OC=CH), 160.73 (s, Ar-OMe), 169.91 (s, C=O).

5-(4-Bromobenzylidene)-5H-furan-2-one (4d). Starting material (**2d**) (440 mg, 1.5 mmol). m.p.: 77 °C (yellow solid). **IR** (KBr): $\tilde{\nu}$ [cm⁻¹] = 3097, 1747, 1547, 1103, 1072, 1011, 931, 881, 811, 765; **GC/MS** (80 eV): m/z (%) = 251 ([M]⁺, 100), 221 (3), 170 (18), 143 (16), 115 (100), 89 (34), 63 (12), 53 (5); **Z-4d**: ¹H NMR (CDCl₃): δ = 5.98 (s, 1 H, OC=CH), 6.20 (dd, 1 H, *J* = 5.3 Hz, *J* = 0.7 Hz, COCH=CH), 7.46-7.57 (m, 2 H, Ar-H), 7.51 (d, 1 H, *J* = 5.3 Hz, COCH=CH), 7.59-7.70 (m, 2 H, Ar-H); ¹³C NMR (CDCl₃): δ = 113.28 (d, OC=CH), 118.94 (d, COCH=CH), 124.07 (s, C_{arom}), 132.46 (d, CH_{arom}), 132.16 (s, C_{arom}), 145.65 (d, COCH=CH), 149.16 (s, OC=CH), 170.32 (s, C=O); **E-4d**: ¹H NMR (CDCl₃): δ = 6.44 (dd, 1 H, *J* = 5.6 Hz, *J* = 1.7 Hz, COCH=CH), 6.76 (s, 1 H, OC=CH), 7.55-7.80 (m, 5 H, COCH=CH, Ar-H); ¹³C NMR (CDCl₃): δ = 114.52 (d, OC=CH), 120.61 (s, C_{arom}), 122.42 (d, COCH=CH), 132.39 (d, CH_{arom}), 133.81 (s, C_{arom}), 141.49 (d, COCH=CH), 150.78 (s, OC=CH), 169.45 (s, C=O).

Method B

The reaction was conducted under argon. To generate the iminium salt, a solution of 1-(α -aminoalkyl)benzotriazole^{11,24} (1.0 mmol) in anhyd MeCN (5 mL) was cooled to 0 °C. AlCl₃ (400 mg, 3.0 mmol) was added in one portion under stirring. After a reaction time of 1 h at this temperature (furan-2-yloxy)trimethylsilane (**1**) (0.16 mL, 1.0 mmol) was added. Stirring was continued for 2 h and the temperature was allowed to rise to 20 °C. To complete the reaction the mixture was heated under reflux for 2 h. Afterwards the mixture was quenched with aq HCl (37% HCl-H₂O, 1:1, 15 mL) and stirred for additional 10 min. The product was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers were dried with Na₂SO₄. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel (CH₂Cl₂, CH₂Cl₂-MeOH, 95:5).

Ethyl (5-Oxo-5H-furan-2-ylidene)acetate (4e). ethyl benzotriazol-1-yl-dimethylamino-acetate (250 mg, 1.0 mmol). m.p.: 74 °C (yellow solid). Lit.²⁹ m.p.: 75-77 °C. **IR** (KBr): $\tilde{\nu}$ [cm⁻¹] = 3440, 1729, 1639, 1421, 1265, 894, 739, 706; **Z-4e**: ¹H NMR (CDCl₃): δ = 1.25 (t, 3 H, *J* = 7.1 Hz, CH₂CH₃), 4.18 (q, 2 H, *J* = 7.1 Hz, CH₂CH₃), 5.85 (s, 1 H, OC=CH), 6.38-6.49 (m, 1 H, COCH=CH), 8.32 (d, 1 H, *J* = 5.5 Hz, COCH=CH); ¹³C NMR (CDCl₃): δ = 14.48 (q, CH₂CH₃), 61.48 (t, CH₂CH₃), 102.97 (d, OC=CH), 124.78 (d, COCH=CH), 142.42 (d, COCH=CH), 160.59, 165.14, 168.18 (s, OC=CH, C=O); **E-4e**: ¹H NMR (CDCl₃): δ = 1.25 (t, 3 H, *J* = 7.1 Hz, CH₂CH₃), 4.18 (q, 2 H, *J* = 7.1 Hz, CH₂CH₃), 5.47 (s, 1 H, OC=CH), 6.38-6.49 (m, 1 H, COCH=CH), 7.59 (d, 1 H, *J* = 5.2 Hz, COCH=CH); ¹³C NMR (CDCl₃): δ = 14.48 (q, CH₂CH₃), 61.48 (t, CH₂CH₃), 102.30 (d, OC=CH), 124.11 (d, COCH=CH), 145.48 (d, COCH=CH), 156.79, 163.44, 168.72 (s, OC=CH, C=O).

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