



## A new synthesis of alkyl (*E*)-(3-dimethylamino)acrylates

Jeffrey M. Robertson, Ian W. Jones, Kevin M. Kayne, Cristina G. Contreras, Daniel J. Witter, Robert B. Bates\*, H. K. Hall Jr.

C. S. Marvel Laboratories, Department of Chemistry and Biochemistry, The University of Arizona, Tucson, AZ 85721, United States

### ARTICLE INFO

#### Article history:

Received 16 April 2011

Revised 26 August 2011

Accepted 1 September 2011

Available online 7 September 2011

#### Keywords:

Acrylates

Dimethylformamide

Ketene acetals

New synthetic method

Vilsmeier reagent

### ABSTRACT

A highly stereoselective one-step method for the synthesis of alkyl (*E*)-(3-dimethylamino)acrylates from *N,N*-dimethylformamide and ketene acetals is reported.

© 2011 Elsevier Ltd. All rights reserved.

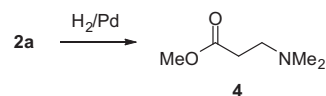
### Introduction

We wish to report a highly stereoselective one-step synthesis of alkyl (*E*)-(3-dimethylamino)acrylates **2** from ketene acetals **1**, *N,N*-dimethylformamide (DMF), and thionyl chloride (Scheme 1). The reaction was discovered when we were trying to prepare something else by a procedure involving these three reactants. Acrylates **2a**<sup>1</sup> and **2b**<sup>2</sup> have been synthesized previously, while acrylate **2c** is new.

### Discussion

The NMR spectra of products **2a–c** in CDCl<sub>3</sub> were complicated by exchange-broadening of the peaks for the *N*-methyl protons, which gave broad peaks at  $\delta$  2.84 integrating for six protons for all three compounds. This exchange-broadening led us to consider the dimethylamide structures **3a–c**, but the ester structures **2a–c** are vinylogous amides which have also been shown to also exhibit exchange-broadening of *N*-methyl protons.<sup>3</sup> Our <sup>1</sup>H NMR shifts matched the literature shifts of the ester structures **2a**<sup>1</sup> and **2b**<sup>2</sup>; the final proof that we had ester structures **2a–c** was that hydrogenation of the methyl compound **2a** with a palladium catalyst gave methyl 3-(dimethylamino)propionate **4**, identified by its <sup>1</sup>H NMR spectrum.<sup>4</sup> The coupling constants between the vinyl hydrogens

in **2a–c** were 12.5–13.0 Hz, indicating *trans* double bonds; there was no evidence for the presence of *cis* double bonds.



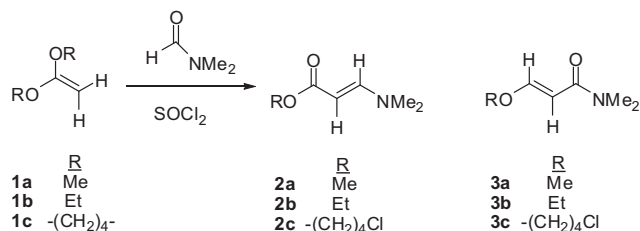
Possible mechanisms for these reactions are shown in Scheme 2. Dimethylformamide reacts with thionyl chloride to give Vilsmeier reagent **5**,<sup>5</sup> which reacts with ketene acetals **1a–c** to give salts **6a–c**. Salts **6a** and **6b** lose RCl to give chlorides **7a** and **7b**, while salt **6c** rearranges to dichloride **7c**. Chlorides **7a–c** lose HCl to give the observed products **2a–c**.

Support for Vilsmeier reagent **5** as an intermediate was obtained by reacting commercial reagent **5** with ketene diethyl acetal **1b** and obtaining ester **2b** in 27% yield. The yield was based on Vilsmeier reagent **5**; since some ketene acetal was polymerizing, it was used in excess. Cyclic ketene acetal **3b** with Vilsmeier reagent **5** gave a mixture of **2c** and the corresponding alcohol with Cl replaced by OH in low yield. The Vilsmeier yields would presumably have been better if the reaction had been run in a dry box, since Vilsmeier reagent **5** decomposes very rapidly in moist air. Acrylates **2a–c** are slowly decomposed by water, so any washing of their solutions in organic solvents should be done quickly with ice-water.

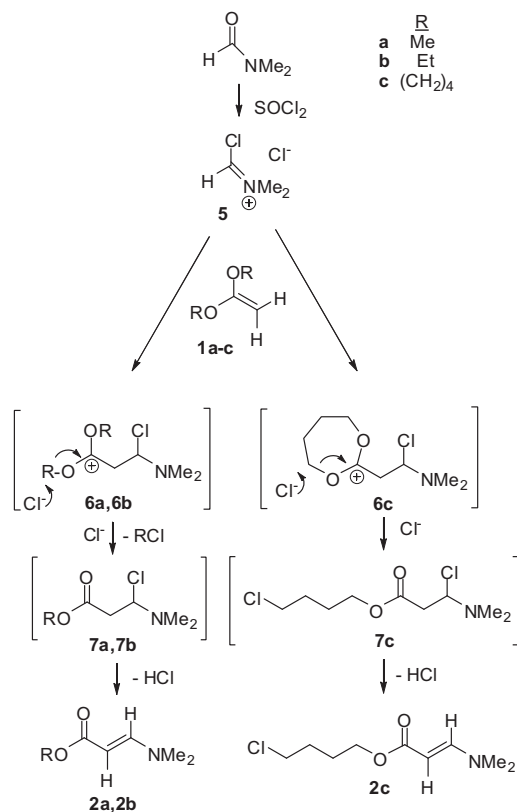
These reactions show that a variety of alkyl (*E*)-(3-dimethylamino)acrylates **2** can be synthesized in one step from ketene acetals by this method.

\* Corresponding author. Address: 1306 East University Boulevard, Tucson, AZ 85721, United States. Tel.: +1 520 621 6317; fax: +1 520 621 8407.

E-mail address: [batesr@u.arizona.edu](mailto:batesr@u.arizona.edu) (R.B. Bates).



**Scheme 1.** Synthesis of alkyl (*E*)-3-(dimethylamino)acrylates **2a–c**; alternative structures **3a–c**.



**Scheme 2.** Possible mechanisms for syntheses of acrylates **2a–c**.

## Experimental

General procedure for **2a–c**: A mixture of thionyl chloride (3 mL, 41 mmol), 4-hydroxybenzoic acid (500 mg, 3.6 mmol), and DMF (7.2 mmol) was stirred until all the acid dissolved (ca 15 min). Excess thionyl chloride was blown off with  $\text{N}_2$ , leaving a white precipitate. Toluene (3 mL) was added and the mixture was stirred to make a suspension, which was added dropwise to a base-washed flask containing triethylamine (5 mL, 36 mmol) and the ketene acetal **1a–c**<sup>6,7</sup> (72 mmol) at 0 °C. The reaction was

stirred at 25 °C for 16 h, poured into ice-water (50 mL) and immediately extracted with ether ( $3 \times 50$  mL). The ether was evaporated and the residual oil was chromatographed on silica gel, eluting with 20% EtOAc/hexanes.  $^1\text{H}$  NMR spectra at 500 MHz and  $^{13}\text{C}$  spectra at 125 MHz were recorded in  $\text{CDCl}_3$  on a Bruker DRX 500 spectrometer. Electron impact ( $\text{EI}^+$ ) mass spectra were run on an Agilent Technologies 6890 N Network GC/MS System.

Methyl (*E*)-(3-dimethylamino)acrylate **2a**: 28% yield.  $^1\text{H}$  NMR:  $\delta$  2.84 (br s,  $\text{NCH}_3$ ), 3.63 (s,  $\text{OCH}_3$ ), 4.49 (d,  $J = 13.0$  Hz,  $\text{CH}=\text{CHN}$ ), 7.41 (d,  $J = 13.0$  Hz,  $\text{CH}=\text{CHN}$ ).  $^{13}\text{C}$  NMR:  $\delta$  50.48 ( $\text{OCH}_3$ ), 84.00 ( $\text{CH}=\text{CHN}$ ), 152.98 ( $\text{CH}=\text{CHN}$ ), 169.45 ( $\text{C}=\text{O}$ ).  $\text{EI}^+$  MS:  $m/z$  129.0794 (calcd for  $\text{C}_6\text{H}_{11}\text{O}_2\text{N}$ : 129.0790).

Ethyl (*E*)-(3-dimethylamino)acrylate **2b**: 29% yield.  $^1\text{H}$  NMR:  $\delta$  1.22 (t,  $J = 7.2$  Hz,  $\text{CCH}_3$ ), 2.84 (br s,  $\text{NCH}_3$ ), 4.09 (q,  $J = 7.2$  Hz,  $\text{CH}_2$ ), 4.48 (d,  $J = 12.5$  Hz,  $\text{CH}=\text{CHN}$ ), 7.40 (d,  $J = 12.5$  Hz,  $\text{CH}=\text{CHN}$ ).  $^{13}\text{C}$  NMR:  $\delta$  14.60 ( $\text{CCH}_3$ ), 58.80 ( $\text{CH}_2$ ), 84.28 ( $\text{CH}=\text{CHN}$ ), 152.86 ( $\text{CH}=\text{CHN}$ ), 169.64 ( $\text{C}=\text{O}$ ).  $\text{EI}^+$  MS:  $m/z$  143.0961 (calcd for  $\text{C}_7\text{H}_{13}\text{O}_2\text{N}$ : 143.0946).

4-Chlorobutyl (*E*)-(3-dimethylamino)acrylate **2c**: 49% yield.  $^1\text{H}$  NMR:  $\delta$  1.76 (p,  $J = 5.6$  Hz,  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 1.84 (p,  $J = 5.6$  Hz,  $\text{OCH}_2\text{CH}_2$ ), 2.85 (br s,  $\text{NCH}_3$ ), 3.55 (t,  $J = 6.5$  Hz,  $\text{CH}_2\text{Cl}$ ), 4.08 (t,  $J = 6.5$  Hz,  $\text{OCH}_2$ ), 4.47 (d,  $J = 13.0$  Hz,  $\text{CH}=\text{CHN}$ ), 7.40 (d,  $J = 13.0$  Hz,  $\text{CH}=\text{CHN}$ ).  $^{13}\text{C}$  NMR:  $\delta$  26.49 ( $\text{CH}_2\text{CH}_2\text{Cl}$ ), 29.37 ( $\text{OCH}_2\text{CH}_2$ ), 44.69 ( $\text{CH}_2\text{Cl}$ ), 61.96 ( $\text{OCH}_2$ ), 83.94 ( $\text{CH}=\text{CHN}$ ), 152.90 ( $\text{CH}=\text{CHN}$ ), 169.45 ( $\text{C}=\text{O}$ ).  $\text{EI}^+$  MS:  $m/z$  205.0634 (calcd for  $\text{C}_9\text{H}_{14}\text{O}_3\text{Cl}$ : 205.0631).

Ester **2b** from Vilsmeier reagent **5**: A mixture of anhydrous  $\text{K}_2\text{CO}_3$  (2 mg), triethylamine (1 mL), ketene diethyl acetal, (**1b**, 0.5 mL) and Vilsmeier reagent **5** (179 mg; large chunks were broken up) was heated and stirred at 60 °C. After 1 h, more **1b** (0.5 mL) was added. After 2 h more, the mixture was cooled and extracted with hexanes ( $3 \times 10$  mL). Evaporation of the hexanes gave ester **2b** (55 mg, 27%).

Methyl 3-(dimethylamino)propionate **4**: Acrylate **2a** (10 mg) in methanol (5 mL) was stirred with 10% Pd/C (10 mg) under a hydrogen atmosphere for 3 h. Filtering and evaporating gave methyl 3-(dimethylamino)propionate (**4**, 10 mg, 100%,  $^1\text{H}$  NMR as reported<sup>4</sup>).

## Acknowledgments

We thank Prof. Tarek Sammakia, University of Colorado, for suggesting structures **2a–c**, and Solvay Advanced Polymers, Alpharetta, GA, for financial support.

## References and notes

- Neuenschwander, M.; Hafner, K. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 460.
- Truce, W. E.; Brady, D. G. *J. Org. Chem.* **1966**, *31*, 3543–3555.
- Landau, M. *Izvestia Akad. Nauk SSSR* **1969**, *9*, 2053–2055.
- Pouchert, C.; Behnke, J. *Aldrich Library of  $^{13}\text{C}$  and  $^1\text{H}$  FT NMR Spectra*; Aldrich Chemical Co.: Milwaukee, 1993. Vol. 1, p. 1070 B..
- Vilsmeier reagent **5** was purchased from Aldrich Chemical Co. For a review of the Vilsmeier reaction, see Jones, G.; Stanforth, S. P. *Organic Reactions*; Hoboken, NJ, 2000; Vol. 56.
- Ketene dimethyl acetal (**1a**) was prepared by the method of Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570–5583.
- Ketene acetals **1b** and **1c** were purchased from Wacker Organics, Adrian, MI.