Organic Process Research & Development **2008,** *12,* 736–739

Concise Synthesis of Vinylheterocycles through β-Elimination under Solventless Phase Transfer Catalysis Conditions

Domenico Albanese,*[,†] Cristina Ghidoli,[†] and Maurizio Zenoni[‡,§]

Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, via Venezian 21, 20133 Milano, and ACS DOBFAR SPA, Viale Addetta, 4/12, 20067 Tribiano, Milano, Italia

Abstract:

Various vinylheterocycles compounds have been prepared in excellent yields through β-elimination of the corresponding sulfonate esters with 50% aq NaOH under phase transfer catalysis conditions without organic solvent. The new approach provides an economic and environmentally friendly solution to removal of hazardous bases as well as toxic and expensive dipolar aprotic solvents.

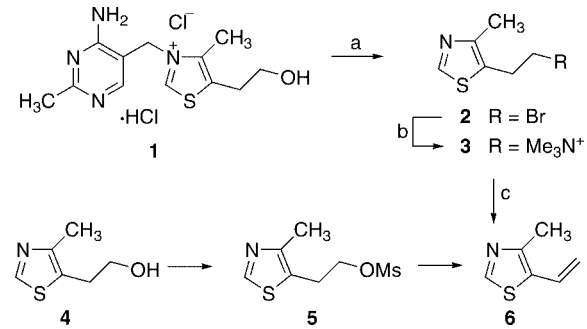
The development of environmentally friendly synthetic procedures has seen a steadily growing interest in the past few years in academic and industrial chemistry.[1] In particular, it is of increasing interest to avoid solvents by carrying out reactions under solvent-free conditions or by replacing them with greener alternatives.[2]

Vinylthiazoles are useful intermediates for the synthesis of pharmaceuticals,[3] flavoring materials,[4] insect repellents[5] and lubricant additives.[6] For example 4-methyl-5-vinylthiazole (**6**), a widely employed vinylthiazole, has been prepared by treating thiamine **1** with saturated aqueous HBr, followed by quaternarization of the resulting bromide **2** with trimethylamine. The vinylthiazole **6** was generated by the sequential treatment of the ammonium salt **3** with Ag_2O and hot KOH (Scheme 1).[7]

This procedure suffers from low atom efficiency since the (4-amino-2-methyl-5-pyrimidinyl)methyl] portion of thiamine is lost. Moreover, the use of corrosive HBr, expensive Ag_2O and toxic benzene severely hinders the scale-up.

More recently vinylthiazoles have also been prepared from the corresponding sulfonate ester **5** through β-elimination promoted by strong bases such as NaH, *t*-BuOK or DBU in DMF (Scheme 1).[5] Although this procedure affords the desired

Scheme 1[a]



[a] Reagents and conditions: (a) HBr 53%, 100°C, 12 h. (b)Me_3N, benzene 100 °C, 12 h. (c) Ag_2O, 1 h; KOH, reflux, 0.5 h.

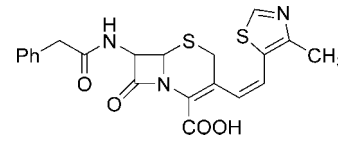


Figure 1. **Cefditoren.**

vinylthiazoles in good yields, it also suffers from limitations derived from using strong but expensive bases that require careful handling. Moreover, process unfriendly solvents such as DMF are required; therefore, additional steps are needed for its removal and disposal.

On the other hand, 5-formyl-4-methylthiazole (**9**) is an important starting material for manufacturing Cefditoren, a wide spectrum antibiotic (Figure 1).[8]

5-Formyl-4-methylthiazole (**9**) has usually been prepared by oxidation of 4-methyl-5-(2-hydroxyethyl)thiazole (**4**) with pyridinium dichromate[9] or other chromium derivatives,[10] or by oxidation of alcohol **8** with MnO_2 [11] or NaOCl (Scheme 2).[12] The aldehyde **9** has also been prepared through reduction of 4-methylthiazole-5-carboxylic acid ethyl ester (**7**) with $NaBH_4-AlCl_3$ followed by oxidation of the alcohol **8** thus

* Author to whom correspondence may be sent. E-mail: domenico.albanese@unimi.it.

† Università degli Studi di Milano.

‡ ACS DOBFAR SPA.

§ Present address: Chemi SpA, via dei Lavoratori, 54, 20092 Cinisello Balsamo, Milano, Italia.

(1) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry, Theory and Practice*; Oxford University Press: Oxford, 1998. (b) Clark, J.; Macquarrie, D. M. A. *Handbook of Green Chemistry & Technology*; Blackwell: Oxford, 2002.

(2) Kochi, M., Ed. *Green Reaction Media for Organic Synthesis*; Blackwell: Oxford, 2005.

(3) Hamze, A.; Rubi, E.; Arnal, P.; Boisbrun, M.; Carcel, C.; Salom-Roig, X.; Maynadier, M.; Wein, S.; Vial, H.; Calas, M. *J. Med. Chem.* **2005**, *48*, 3639–3643.

(4) Piggott, J. R.; Paterson, A.; Conner, J. M.; Haack, G. *Dev. Food Sci.* **1993**, *32*, 521–532.

(5) Kameyama, Y. JP Pat. 313 174; *Chem. Abstr.* **2003**, *139*:350730.

(6) Sauer, R. P. U.S. Patent 205,611; *Chem. Abstr.* 2006, *145*:338711.

(7) (a) Buchman, E. R.; Richardson, E. M. *J. Am. Chem. Soc.* **1945**, *67*, 395–399. (b) D'Auria, M.; Esposito, V.; Mauriello, G. *Tetrahedron* **1996**, *52*, 14253–14272.

(8) (a) Sakagami, K.; Atsumi, K.; Tamura, A.; Yoshida, T.; Nishihata, K.; Fukatsu, S. *J. Antibiot.* **1990**, *43*, 1047–1050. (b) Okada, Y.; Sukegawa, M.; Watanabe, T.; Iwasawa, H.; Murai, Y.; Iinuma, K. PCT Int. Appl. WO 98 58932, 1998; *Chem. Abstr.* **1999**, *130*:81348x. (c) Kasai, M.; Hatano, S.; Nishimura, K.; Kakeya, N. PCT Int. Appl. WO 98 58933, 1998; *Chem. Abstr.* **1999**, *130*:95424f.

(9) White, R. L.; Spenser, I. D. *J. Am. Chem. Soc.* **1982**, *104*, 4934–4943.

(10) Yarkevich, A. N.; Safronova, Z. V.; Pushin, A. N.; Ragulin, V. V.; Zefirov, N. S. JP Pat. 107 346. *Chem. Abstr.* **2004**, *140*, 303659.

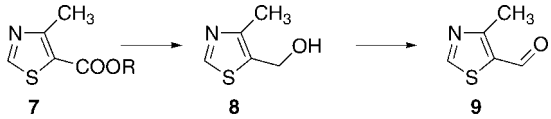
(11) Kumar, Y.; Prasad, M.; Singh, K.; Prasad, A.; Richhariya, S. WO 100 330; *Chem. Abstr.* **2005**, *143*:440152.

(12) (a) Deshpande, P. B.; Luthra, P. K.; Vyas, R.; Kamma, R.; U.S. Patent 6,833,459, 2004; *Chem. Abstr.* **2003**, *139*:337963. (b) Tanaka, H.; Chou, J.; Mine, M.; Kuroboshi, M. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1745–1755.

Published on Web 03/19/2008

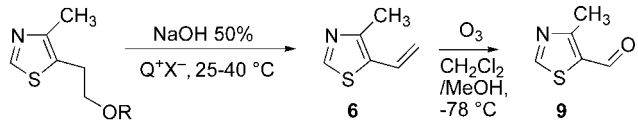
10.1021/op800001d CCC: $40.75

Scheme 2



R = Me, Et

Scheme 3



4 R = H

5 R = Ms

$MsCl/CH_2Cl_2$, 25 °C, 99%

***Table 1. β*-Elimination of 5 under LL-PTC conditions**

entry	cat. (mol %)	base (equiv)	*T* (°C)	*t* (h)	yield (%)
1	TEBA (5)	50% NaOH (5)	25	2.5	90
2[a]	TEBA (5)	50% NaOH (5)	25	6	85
3	TEBA (2.5)	50% NaOH (5)	40	6	76
4	TEBA (2.5)	50% NaOH (3)	40	6	70
5	$C_{14}H_{29}Me_2BnN^+Cl^-$ (2.5)	50% NaOH (3)	40	5	89
6	Aliquat 336 (2.5)	50% NaOH (5)	25	2	90
7	$Bu_4N^+HSO_4^-$ (2.5)	50% NaOH (3)	40	4	90
8	–	50% NaOH (5)	25	24	–
9	TEBA (5)	40% NaOH (5)	25	24	<5

[a] In toluene as solvent.

obtained.[12] The direct reduction of ester **7** to aldehyde **9** has been carried out with Red-Al in moderate yield.[13] All these methods suffer from limitations derived from the use of hydride reducing agents or metal reagents that produce significant waste. Moreover, starting compounds **7** and **8** are not readily available.

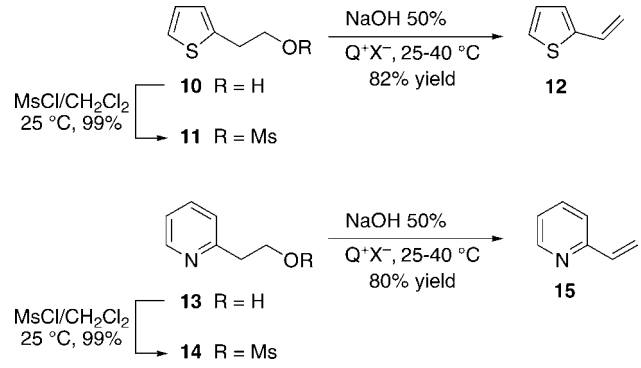
Discussion

We report that the elimination of sulfonate ester **5** can be very efficiently carried out in the absence of any organic solvent by using inexpensive inorganic base such as 50% aq NaOH under liquid–liquid phase transfer catalysis (LL-PTC) conditions (Scheme 3). 4-Methyl-5-vinylthiazole (**6**) was isolated in excellent yields or directly converted into aldehyde **9** in good overall yields by ozonolysis.

The intermediate 4-methyl-5-thiazoleethanol *O*-methanesulfonate (**5**) was prepared in quantitative yield through a standard mesylation procedure in CH_2Cl_2. Good results have also been obtained without solvent; however, care should be taken in order to control the exothermic reaction and maintain efficient stirring of the reaction mixture.

The β-elimination reaction has been carried out by dropwise addition of 50% NaOH to a stirred mixture of mesylate **5** and $Et_3BnN^+Cl^-$ (TEBA, 5 mol%) at 25 °C. Complete conversion of substrate was reached in a short time without organic solvent generating a 90% yield of 4-methyl-5-vinylthiazole (**6**) (Table 1, entry 1). The latter can be isolated after dilution with water, followed by phase separation and purification by distillation. A slightly lower yield of **6** was generated over a longer reaction time when mesylate **5** was dissolved in toluene (Table 1, entry 2).

Scheme 4



As expected, the reaction rate increases with NaOH concentration. In fact 40% NaOH proved to be ineffective (entry 9). This behaviour is in agreement with the well-known higher reactivity of concentrated alkaline solution, from the low hydration state of hydroxide anion.[14] Complete conversions of mesylate **5** have also been achieved at 40 °C by using a lower excess of 50% NaOH (entries 5,7).

The reaction does require phase transfer catalyst (Table 1, entry 8) and the reaction rate gradually increases with the amount of catalyst as expected in the case of a PTC process.[15] Various catalysts perform well in the β-elimination reaction. The best results have been obtained with TEBA and $Bu_4N^+HSO_4^-$which are also easily removed during workup.

No significant hydrolysis of the sulfonate ester **5** derived from nucleophilicity of hydroxide anion have been detected in the presence of 50% NaOH under PTC conditions. This trend can be ascribed to the low extractability of hydroxide anion in the organic phase and its remarkable reactivity when largely dehydrated as in 50% NaOH.[16]

The reaction scope has been investigated by using 2-thiopheneethanol (**10**) and 2-pyridineethanol (**13**) as model compounds (Scheme 4).

2-Vinylthiophene (**12**) and 2-vinylpyridine (**15**) have been isolated in good overall yields under the previously described reaction conditions, clearly indicating the generality of the procedure.

With a straightforward method for the synthesis of 4-methyl-5-vinylthiazole (**6**) in hand, we turned our attention to its conversion into the corresponding aldehyde **9** in order to overcame drawbacks related to the reductive/oxidative pathways previously described.[9–13] Thus, crude vinylthiazole **6** was diluted with MeOH and subjected to ozonolysis at −78 °C. After quenching with aqueous Na_2SO_3 and a standard workup, the desired aldehyde was isolated in 84% overall yield.

In summary, the use of catalytic amounts of a quaternary ammonium salt provides a practical, high-yield method for the synthesis of various vinyl derivatives such as **6**,**12**, and **15**,

(13) Hagiya, K.; Mitsui, S.; Taguchi, H. *Synthesis* **2003**, 823–828.

(14) Albanese, D.; Landini, D.; Maia, A.; Penso, M. *Ind. Eng. Chem. Res.* **2001**, *40*, 2396–2401.

(15) (a) Starks, M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994. (b) Dehmlow, E. V.; Dehmlow; S. S. *Phase Transfer Catalysis*; Verlag Chemie: Weinheim, 1993.

(16) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1986**, *51*, 5475–5476.

valuable intermediates for the synthesis of bioactive and industrially important compounds. No organic solvent is required during the β-elimination procedure, pure products can be isolated quickly by phase separation followed by distillation, and only nonhazardous and inexpensive compounds are used. We anticipate that the mild conditions employed in the new procedure will allow it to be used for the large-scale synthesis of a large number of substrates.

Experimental Section

General Remarks. Substrates **4**,**10**, and **13** are commercially available. Pellets of NaOH were ground in a mortar before use. NMR spectra were recorded on a Bruker AC 300 or AC 200 spectrometer, operating at 300.13 or 200.13 MHz for ^{1}H NMR and 75.3 or 50 MHz for ^{13}C NMR. Chemical shifts are reported by using $CHCl_3$ as an external standard ($\delta = 7.24$ ppm for ^{1}H NMR and 77.0 for ^{13}C NMR). The coupling constants J are given in hertz. APT experiments were used in the assignment of carbon spectra.

4-Methyl-5-thiazoleethanol *O*-Methanesulfonate (5). *Method A.* 4-Methyl-5-thiazoleethanol (**4**) (25.1 g, 0.18 mol) was dissolved in CH_2Cl_2 (70 mL) and cooled in a water/ice cooling bath. After addition of Et_3N (20.24 g, 0.20 mol) methanesulfonyl chloride (22.9 g, 0.20 mol) was added dropwise over 15 min at the same temperature. After stirring at room temperature for 4 h, the reaction mixture was diluted with sat. $NaHCO_3$, and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL), and the combined extracts were washed with water and dried over Na_2SO_4; the solvent was removed at reduced pressure to give **5** (38.30 g, 99%) as a colourless oil that solidified on standing at 0 °C (Calcd for $C_7H_{11}NO_3S_2$: C, 37.99; H, 5.01; N, 6.33. Found: C, 38.1; H, 5.02; N, 6.35.); ^{1}H NMR ($CDCl_3$): δ 2.43 (3 H, s), 2.96 (3 H, s), 3.23 (2 H, t, J 9.9), 4.36 (2 H, t, J 9.9), 8.63 (1 H, s).

Method B. 4-Methyl-5-thiazoleethanol (**4**) (25.1 g, 0.18 mol) was cooled to 0 °C, and Et_3N (20.24 g, 0.20 mol) was added dropwise over 15 min. Methanesulfonyl chloride (22.9 g, 0.20 mol) was added dropwise over 60 min at the same temperature. After stirring at room temperature for 4 h, the reaction mixture was diluted with sat. $NaHCO_3$, and the two phases were separated. The organic phase was washed with brine (20 mL) and dried over Na_2SO_4 to give **5** (35.6 g, 92%) as a yellowish oil.

2-Thiopheneethanol *O*-Methanesulfonate (11). 2-Thiophene ethanol (**10**) (12.8 g, 0.1 mol) was dissolved in CH_2Cl_2 (50 mL) and cooled in a water/ice cooling bath. Et_3N (12.1 g, 0.12 mol) was added, and then methanesulfonyl chloride (13.7 g, 0.12 mol) was added dropwise over 15 min at the same temperature. After stirring at room temperature for 2 h the reaction mixture was diluted with sat. $NaHCO_3$, and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined extracts were washed with water (20 mL) and dried over Na_2SO_4; the solvent was removed at reduced pressure to give **11** (20.4 g, 99%) as a colourless oil (Calcd for $C_7H_{10}O_3S_2$: C, 40.76; H, 4.89. Found: C, 40.86; H, 4.91); ^{1}H NMR ($CDCl_3$): δ 2.46 (3 H, s), 2.93 (3 H, s), 3.28 (2 H, t, J 6.7), 4.42 (2 H, t, J 6.7), 6.91–6.96 (2 H, m), 7.20 (1 H, dd, J 1.3 and 5.1).^{13}C NMR ($CDCl_3$): 29.8, 37.4, 69.7, 124.5, 126.2, 127.0, 138.12.

2-Pyridineethanol *O*-Methanesulfonate (14). 2-Pyridine ethanol (**13**) (12.3 g, 0.1 mol) was dissolved in CH_2Cl_2 (50 mL) and cooled in a water/ice cooling bath. Et_3N (12.1 g, 0.12 mol) was added, and methanesulfonyl chloride (13.7 g, 0.12 mol) was added dropwise over 15 min at the same temperature. After stirring at room temperature for 3 h, the reaction mixture was diluted with sat. $NaHCO_3$, and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL), and the combined extracts were washed with water (20 mL) and dried over Na_2SO_4; the solvent was removed at reduced pressure to give **14** (19.7 g, 98%) as a colourless oil (Calcd for $C_8H_{11}NO_3S$: C, 47.75; H, 5.44, N, 6.96. Found: C, 47.86; H, 5.42, N, 6.94); ^{1}H NMR ($CDCl_3$): δ 2.91 (3 H, s), 3.26 (2 H, t, J 6.3), 4.67 (2 H, t, J 6.3), 7.15–7.21 (2 H, m), 7.62 (1 H, dt, J 1.9 and 7.7), 8.57 (1 H, m).

4-Methyl-5-vinylthiazole (6). To a mixture of mesylate **5** (37.62 g, 0.17 mol) and $Et_3BnN^+Cl^-$ (1.94 g, 0.085 mol) was added 50% NaOH (45 mL) with vigorous magnetic stirring at <40 °C. After 2.5 h, the reaction mixture was cooled to 0–5 °C, and water (80 mL) was dropwise added over 15 min at <15 °C. After dilution with water (50 mL) the organic phase was separated, diluted with CH_2Cl_2 (20 mL) and washed with sat. NH_4Cl. The organic phase was separated, phenothiazine was added as a polymerization inhibitor, and the mixture was distilled under vacuum (bp 65 °C, 20 mmHg; lit.,[7b] 78–80 °C, 25 mmHg) to give **6** (19.15 g, 90%) as a colourless oil (Anal. Calcd for C_6H_7NS: C, 57.56; H, 5.64; N, 11.19. Found: C, 57.65; H, 5.62; N, 11.16); ^{1}H NMR ($CDCl_3$): δ 2.46 (3 H, s), 5.28 (1 H, d, J 10.9), 5.50 (1 H, d, J 17.2), 6.82 (1 H, dd, J 10.9 and 17.2), 8.55 (1 H, s).

*2-Vinylthiophene (**12**).* Under the same reaction conditions as described for the synthesis of **6**, 50% NaOH (13.2 mL) was added dropwise to a mixture of **11** (10.31 g, 50 mmol) and $Et_3BnN^+Cl^-$ (0.57 g, 2.5 mol). The reaction mixture was stirred at 40 °C for 5 h. After the usual workup, the residue was distilled (64–65 °C, 50 mmHg; lit,[17] 65.5–66.5 °C, 48 mmHg) to give **12** (4.52 g, 82%) as a colourless oil. (Anal. Calcd for C_6H_6NS: C, 65.41; H, 5.49; N, 29.10. Found: C, 65.53; H, 5.47; N, 29.17.). ^{1}H NMR ($CDCl_3$): δ 5.13 (1 H, d, J 10.9), 5.56 (1 H, d, J 17.4), 6.80 (1 H, dd, J 10.9 and 17.4), 6.96 (2 H, m), 7.17 (1 H, m). ^{13}C NMR ($CDCl_3$): δ 113.2, 124.3, 125.7, 127.2, 129.8, 143.03.

*2-Vinylpyridine (**15**).* Under the same reaction conditions as described for the synthesis of **6**, 50% NaOH (13.2 mL) was added dropwise to a mixture of **14** (10.06 g, 50 mmol) and $Et_3BnN^+Cl^-$ (0.57 g, 2.5 mol). The reaction mixture was stirred at 40 °C for 2 h (TLC AcOEt/PE, 1:4). After the usual workup, the residue was distilled (64–65 °C, 21 mmHg; lit,[18] 68.5 °C, 23 mmHg) to give **15** (4.21 g, 80%) as a colourless oil (Anal. Calcd for C_7H_7N: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.12; H, 6.68; N, 13.35). ^{1}H NMR ($CDCl_3$): δ 5.48 (1 H, dd, J 1.1 and 10.8), 6.20 (1 H, dd, J 1.1 and 17.5), 6.83 (1 H, dd, J 10.8 and 17.5), 7.15 (1 H, m), 7.35 (1 H, m), 7.65 (1 H, dt, J 1.8 and 7.7), 8.58 (1 H, m).

(17) Schick, J. W.; Hartough, H. D. *J. Am. Chem. Soc.* **1948**, *70*, 1646–1647.
(18) Bauer, L.; Gardella, L. A. *J. Org. Chem.* **1961**, *26*, 82–85.

4-Methyl-5-formylthiazole (9). Crude **6** dissolved in CH_2Cl_2 (10 mL) derived from the β-elimination reaction of **5** (33.20 g, 0.15 mol) described above was used for the synthesis of **9**.

A 3.75 M solution of **6** (40 mL of a 1:3 CH_2Cl_2/MeOH solvent mixture) was cooled to −78 °C, and an O_3/O_2 mixture[19] was bubbled in at 80 L/h (O_3 content 0.8 mmol/min) for 200 min. The temperature was raised to −40 °C, and an aqueous 1.33 M Na_2SO_3 solution was added dropwise (135 mL). After allowing the temperature to increase to 25 °C, the phases were separated, and the aqueous phase was extracted with AcOEt. The combined organic phases were washed with water and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford 16.1 g of **9** (84% overall).

The pure aldehyde **9** can be obtained by sublimation (0.3 mmHg, yield 60%) or crystallisation (AcOEt at −20 °C, yield 75%), mp 74.8–75.2 (lit.,[13] 71 °C) ^{1}H NMR ($CDCl_3$): δ 2.79 (3 H, s), 8.96 (1 H, s), 10.14 (1 H, s).

(19) Ozone was generated with a conventional apparatus; see for example: Barton, M.; Ebdon, J. R.; Foster, A. B.; Rimmer, S. *J. Org. Chem.* **2004**, *69*, 6967–6973.

Acknowledgment

We thank ACS DOBFAR for financial support.

Received for review January 2, 2008.

OP800001D