J.Serb.Chem.Soc. *69*(4)239–245(2004)
JSCS – 3149

UDC 547.789+547.82
Original scientific paper

Facile rearrangement of push-pull 5-substituted 4-oxothiazolidines induced by pyridinium hydrobromide perbromide under homogeneous reaction conditions

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(Received 3 October 2003)

Abstract: Pyridinium hydrobromide perbromide (PHBP) is a highly efficient reagent for the conversion of 5-substituted-2-alkylidene-4-oxothiazolidine derivatives to the corresponding thiazolidines with two fully delocalized exocyclic double bonds at the C(2) and C(5) positions. This conversion as a two-step bromination-rearrangement process occurs in acetonitrile under homogeneous reaction conditions.

Keywords: thiazolidine, rearrangement, pyridinium hydrobromide perbromide, acetonitrile.

INTRODUCTION

A great deal of data is presented in the literature on the functionalization of nitrogen heterocycles containing a β-enamino fragment **1** (Scheme 1) with various electron-withdrawing groups W (CN, COR, CO_2R, CONHAr) at the α-carbon atom.[1–6] We have reported recently a synthesis and *Z*/*E* isomerization study of (*Z*)-5-substituted-2-aklylidene-4-oxothiazolidines **3a–e** (Scheme 2) which belong to the class of functionalized push-pull β-enamines.[7–9] Due to the n, π-interactions between the donor and acceptor groups *via* the polarized C=C group, the increased electron density at the α-carbon atom in these and related compounds is reflected in their enhanced nucleophilicity. A consistent set of high field chemical shifts for the α-carbon atoms (δ 89–95 ppm) and low field shifts for the β-carbon atoms (δ 151–162 ppm) in **3a–e**[10,11] proved the higher electron density of the former atoms.

Therefore, a regiocontrolled α-bromination of compounds with the structural unit **1** affording the α-bromo-α,β-unsaturated carbonyl compounds **2** (Scheme 1), which are synthetically useful α-acylvinyl anion equivalents,[12–15] is to be ex-

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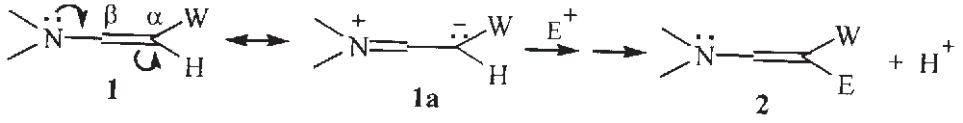
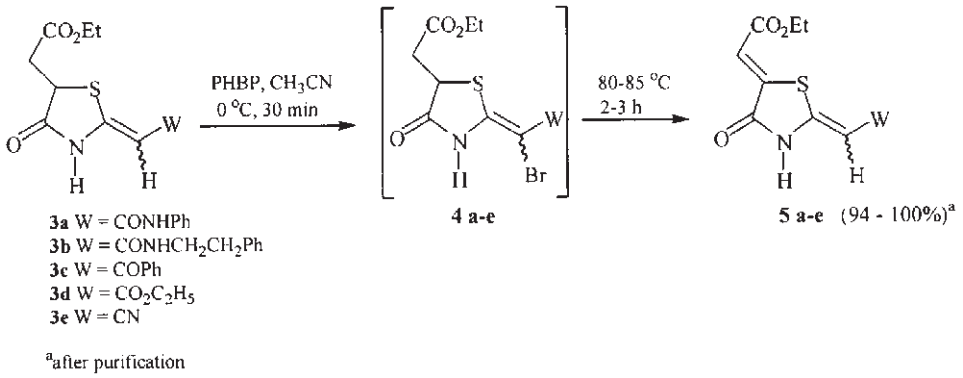


Scheme 1.

pected. This type of molecular bromination-dehydrobromination transformation carried out by various brominating reagents, usually requires a base such as pyridine,[16] DBU,[17] Et_3N,[18,19] DABCO,[20,21] K_2CO_3,[22] or $NaHCO_3$.[23]

RESULTS AND DISCUSSION

In this paper a general and highly efficient bromination-rearrangement conversion of 5-substituted-4-oxothiazolidine derivatives **3** into the corresponding thiazolidines **5** with two fully delocalized exocyclic C=C bonds (Scheme 2) is reported.



Scheme 2.

A mechanistic proposal for this transformation, based on the structural characteristics of the substrates **3** and PHBP is suggested. These studies have been stimulated, in part, due to the diverse biological activity of natural thiazolidines and their synthetic analogues.[24] Additionally, in view of our efforts to develop push-pull heterocyclic polyenes with potential application in electronic devices, we became interested in an expeditious synthesis of thiazolidine precursors **5**.[25]

Previous studies indicated that the α-bromination of **3** [Br_2 in CCl_4, reflux, 30 min (**3b** and **3e**); Br_2 in dry EtOH, r.t., 10 min (**3a** and **3c**)], yielding the α-bromo-α,β-unsaturated compounds **4** (Scheme 2) in moderate yields (60–66 %),[10,11] occurs without base,[26–28] except in the case of **3d** when one equivalent of pyridine is required (Br_2 in $CHCl_3$, r.t., 4 h). Moreover, the preformed vinyl bromides **4a–e** undergo a novel rearrangement upon treatment with excess pyridine giving rise to 4-oxothiazolidine derivatives **5** in a good yield (49–63 %). Thus, the sequential bromination-rearrangement **3**→**4**→**5**, occurring *via* the *in situ* formed vinyl bromides **4**, is induced by PHPB in CH_3CN under homogeneous reaction conditions.

The soluble PHBP in CH_3CN was selected as the halogenating reagent due to its ease of handling and mild reactivity.[29,30] It is also environmentally safer in comparison to elemental bromine. In addition, the amount of bromine is difficult to control, as excess reagent led to overbromination. Table I summarizes the results of the bromination-rearrangement reaction between thiazolidine derivatives **3** and PHBP in CH_3CN.

TABLE I. Synthesis of thiazolidines **5a–e** with two exocyclic C=C bonds from **3a–e**[a] using PHBP under homogenous reaction conditions[b]

Substrate	W	Product[c]	Yield[d]/%	*2Z,5Z*/*2E*,*5Z*[e]	
				Crude product	Purified product
3a	CONHPh	**5a**	quant.	–	37/63
3b	$CONHCH_2CH_2Ph$	**5b**	98	79/21	50/50
3c	COPh	**5c**	quant.	–	10/90
3d	$CO_2C_2H_5$	**5d**	quant.	72/28	32/68
3e	CN	**5e**	94	75/25	79/21

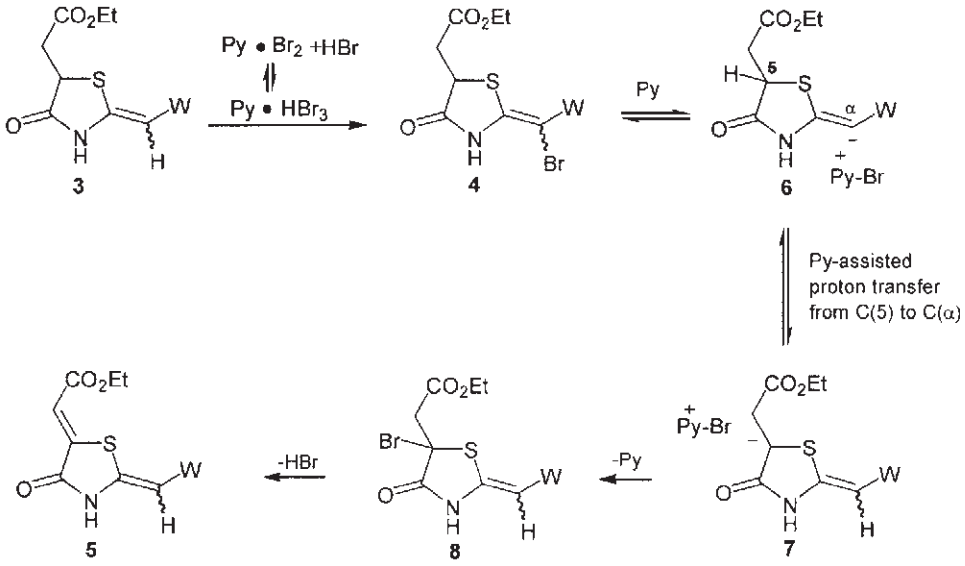
[a]The starting compounds (*Z*)-**3a–3d** and **3e** (*Z*/*E* mixture) were synthesized by a regioselective base-catalyzed reaction of the corresponding β-oxonitriles with diethyl mercaptosuccinate in ethanol under reflux.[8]
[b]The mole ratio of PHBP to thiazolidine substrate **3** was 1.2:1.
[c]All the products were characterized by spectroscopic data (^{1}H-, ^{13}C-NMR, IR, MS, UV) and elemental anlysis.
[d]Yields refer to chromatographically isolated compounds.
[e]The ratio of the configurational isomers, determined by ^{1}H-NMR spectroscopy, depends on the polarity of the eluant used for the column charomatographic purification; (*Z*)-configuration of the exocyclic double bond at C(5) in **5a–e** is fixed due to the repulsive interactions between the lactam carbonyl and the ethoxycarbonyl group in the *E*-configurated isomers.

The method differs markedly from the heterogeneous alternative (PHBP in $CHCl_3$). The use of CH_3CN allows the complete solubility of PHBP, the reactant, each intermediate and the product. As a single phase is utilized, the reactions have rates up to 10 times faster than in $CHCl_3$. The typical sequential transformation **3**→**4**→**5** was carried out in a one-pot procedure by the addition of a 20 % molar excess of PHBP, dissolved in CH_3CN, over a five-minute period to a solution of derivative **3** at 0 ºC in CH_3CN. In all cases, the bromination, monitored by TLC, was completed within half an hour to give the corresponding vinyl bromides **4** as the exclusive intermediates. To facilitate a smooth rearrangement **4**→**5**, the resulting mixture was warmed to 80–85 ºC. After additional stirring (2–3 h), followed by evaporation of the volatiles and purification of the solid residue by silica gel flash chromatography, the products **5** were isolated in nearly quantitative yield. The procedure was found to be highly reproducible.[31] Likewise, treatment of the preformed vinyl bromides **4a–e** with a large excess of pyridine furnished the thiazolidines **5a–e**, but in much lower overall yields.

Purification of the crude products **5a–e** by column chromatography led to mixtures containing, in varying proportions, the 2*Z*,5*Z* and 2*E*,5*Z*-isomers. This is understandable in terms of the facile *Z*/*E* isomerization of the C(2)-exocyclic double bond as an intrinsic structural property of the precursors **3a–e**, as well as of the products **5a–e**. The key factor controlling the *Z*/*E* ratio is the strength of the inter- and intramolecular hydrogen bonds which, among other factors, depends on the medium polarity.[9,32] The diastereomer ratios of the crude and purified products **5a–d** were determined by the integration of the C(α) olefinic protons, or lactam protons which show a consistent difference in chemical shifts.[10,11,31,32]

With the exception of **3e** and **5e** (W = CN), the intramolecularly H-bonded 2*E*,5*Z*-**5a–d** isomers predominate in nonpolar solvents. For example, an equilibrated ratio of *ca.* 10/90 favoring the 2*E*,*5Z*-diastereomer in $CDCl_3$ was determined for **5c** (W = COPh). As a general rule, replacement of a nonpolar solvent by a polar one (DMSO, DMF, CH_3CN) increases the stability and, therefore, the abundance of the 2*Z*,5*Z*-isomers (Table I, columns 5 and 6). The configurational stability of the 2*Z*,5*Z*-isomers is attributed to (1) strong intermolecular H-bonding interactions with the polar solvent and (2) an equally dominant electrostatic oxygen-sulfur interaction of the 1,5-type within the structural unit S–C=C–C=O with the *cis*-configurated C=C bond.[33]

A plausible mechanism for the formation of thiazolidines **5a–e** is depicted in Scheme 3.



Scheme 3.

The first step is α-bromination of the thiazolidine derivatives (*Z*)-**3a–d** (*Z*/*E* mixture in the case of **3e**). Since it is known that Py·HBr_3 is in equilibrium with Py·Br_2 in the presence of alkenes,[34] it is assumed that the latter is the brominating

reagent. The reactions, monitored by TLC, were carried until the disappearance of the starting derivatives. Interestingly, in the case of the (*Z*)-isomers **3a**, **3b** and **3d**, TLC indicated the presence of two spots with quite different R_f values. This experimental result should obviously be ascribed to the facile silica-gel induced *Z*/*E* isomerization.

The rearrangement of the vinyl bromide **4** to **5** starts with the pyridine-assisted heterolytic cleavage of the C–Br bond, leading to an ion-pair **6**, consisting of a vinylogous carbanion and mono(pyridine)bromonium cation. Fast hydrogen transfer, occurring through the pyridine-induced C(5) proton capture and protonation at C(α), forms another carbanion-Br^+-pyridine ion-pair **7**. The simultaneous migration of the bromonium ion (Py-Br^+), from one carbanionic site of the ion pair complex **6** to the other of complex **7**, is actually the consequence of a pyridine-conducted proton transfer from the C(5) atom to C(α). This type of reversible ion pair reorganization based on electrostatic interactions is followed by the irreversible collapse of **7**, occurring by bromination within the ion pair complex **7**. The resulting alkyl bromide **8**, formed as a transient species, was not observed due to its facile pyridine-catalyzed dehydrobromination to product **5**. Surprisingly, the starting thiazolidine **3** was also detected (TLC) during the **4**→**5** rearrangement. The formation of the substrate **3** can be easily explained *via* protonation of the ion-pair **6** and/or **7** by HBr, which is constantly generated during the whole process. Under these conditions Py·Br_2 accumulates, and presumably converts compound **3** to **5** as described.

In conclusion, an easy-to-handle and efficient route to thiazolidines with two exocyclic double bonds from 5-substituted-2-alkylidene-4-oxothiazolidines has been described. Experimental data indicate that the homogenous bromination-rearrangement sequence using soluble PHBP in acetonitrile goes to (1) completion without the need to isolate the α-bromo-α,β-unsaturated intermediate; (2) it offers a simplified procedure which is cleaner and less polluting in comparison to Br_2 (3) the compounds are readily recovered (non-aqueous work-up); and (4) chromatographically isolated yields are very high (94–100 %).

Acknowledgment: Partial financial support from the Ministry of Science, Technology and Development of the Republic of Serbia (grant No. 1709 to R. M.) is acknowledged.

ИЗВОД

ЕФИКАСНО ПРЕМЕШТАЊЕ PUSH-PULL 5-СУПСТИТУИСАНИХ 4-ОКСОТИАЗОЛИДИНА ИНДУКОВАНО ПИРИДИНИЈУМ-ХИДРОБРОМИД--ПЕРБРОМИДОМ ПОД ХОМОГЕНИМ РЕАКЦИОНИМ УСЛОВИМА

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Пиридинијум-хидробромид-пербромид (PHBP) је веома ефикасан реагенс за конверзију 5-супституисаних-2-алкилиден-4-оксотиазолидинских деривата у одговарајуће тиазолидине са две потпуно делокализоване егзоцикличне двогубе везе у положајима C(2) и C(5). Ова конверзија је двофазни процес бромовања и премештања који се одвија у ацетонитрилу под хомогеним реакционим условима.

(Примљено 3. октобра 2003)

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31. (2*E*,5*Z*)- and (2*Z*,5*Z*)-(5-Ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**5c**). According to the typical procedure, from **3c** (61 mg, 0.20 mmol) in CH_3CN (3 mL) and

PHBP (77 mg, 0.24 mmol) in CH_3CN (2 mL), flash chromatography (toluene/EtOAc 6:1) afforded **5c** as a mixture of two diastereoisomers (Table I); yield 60.5 mg (100 %); mp 167–169 ºC. MS (EI): *m*/*z* (rel. intensity) 303 (M^+, 100), 302 (66), 274 (10), 258 (12), 257 (18), 230 (6), 226 (17), 198 (6), 180 (1), 159 (2), 158 (5), 131 (12), 130 (8), 105 (19), 103 (9), 85 (16), 77 (17), 68 (5). IR (KBr) of mixture of 2*Z*,5*Z*- and 2*E*,5*Z*-isomers: ν 3442, 3193, 3079, 2987, 1727, 1689, 1639, 1616, 1550, 1369, 1318, 1220, 1196, 812, 762, 707, 651 cm^{-1}. ^{1}H-NMR (200 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer, distinct signals) = 1.29 (*t*, 3 H, CH_3, J = 7.0 Hz), 4.27 (*q*, 2 H, CH_2O, J = 7.0 Hz), 6.67 [*s*, 1 H, =CH (C2)], 6.97 [*s*, 1 H, =CH (C5)], 7.53–7.65 (*m*, 3 H, *meta* and *para*-phenyl), 7.89–7.94 (*m*, 2 H, *ortho*-phenyl), 12.71 (*s*, 1 H, NH); δ (2*Z*,5*Z*-isomer) = 1.25 (*t*, 3 H, CH_3, J = 7.1 Hz), 4.20 (*q*, 2 H, CH_2O, J = 7.1 Hz), 6.91 [*s*, 1 H, =CH (C2)], 7.05 [*s*, 1 H, =CH (C5)], 7.53–7.65 (*m*, 3 H, *meta* and *para*-phenyl), 7.89–7.94 (*m*, 2 H, *ortho*-phenyl), 12.49 (*s*, 1 H, NH). ^{13}C-NMR (50 MHz, DMSO-d_6); δ (2*E*,5*Z*-isomer) = 14.15 (CH_3), 61.9 (CH_2O), 97.1 [=CH (C2)], 117.3 [=CH (C5)], 128.0 (*ortho*-phenyl), 128.8 (*meta*-phenyl), 133.1 (*para*-phenyl), 137.6 [C(1)-phenyl], 139.5 [C= (C5)], 153.5 [C= (C2)], 165.7 (CO_{ring}), 166.2 (CO_{ester}), 189.0 (CO_{exo}). UV ($CHCl_3$), (for a mixture of two diastereoisomers): λ_{max} (ε) 286 nm (11,400); 368 (29,400). Anal: Calcd. for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62; S, 10.57. Found: C, 59.19; H, 4.24; N, 4.90; S, 10.30.

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