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Synthesis of (Z)-2-Alkylidene-4-oxothiazolidine Derivatives Under Microwave Irradiation

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In comparison to conventional technique, experimental evidence reveals the benefits of the microwave-promoted synthesis of functionalized 4-oxothiazolidine derivatives **4** in terms of simple workup, efficiency and safe reproducibility.

Key Words: 4-Oxothiazolidine, β-Enamines, Microwave irradiation, Solvent-free synthesis.

INTRODUCTION

The advantages of numerous microwave (MW)-induced reactions over conventional reactions and their utility in organic synthesis, have been fully recognized in the last two decades[1-3]. Well-known applications of the MW methodology involve the effective syntheses and functionalization of various and structurally diverse heterocyclic compounds[4]. Among them, a few examples of MW-assisted syntheses of a series of 2-substituted 4-thiazolidinones, based exclusively on the condensation-cyclization sequence employing a three-component reaction mixture of a substituted acyclic or aromatic primary amine or diamine, aldehyde and mercaptoacetic acid, have been described[5-9]. Other common methods to construct a 4-oxothiazolidine skeleton for example, (i) by treatment of α-haloalkanoic acids and their derivatives[10] or dimethyl acetylenedicarboxylate[11] with substituted thioureas, (ii) from ammonium dithiocarbamates and glycidic esters[12] or (iii) by one-pot cyclization of arylacetonitriles with N-phenylisothiocyanate and ethyl 2-chloro-2-oxoacetate[13], are limited to classical liquid-phase synthesis.

In a continuation of our studies on the chemistry of heterocyclic enaminones and enaminonitriles, containing the 4-oxothiazolidine moiety[14-17] which is of broad synthetic and biological relevance[10,18,19], we wish to

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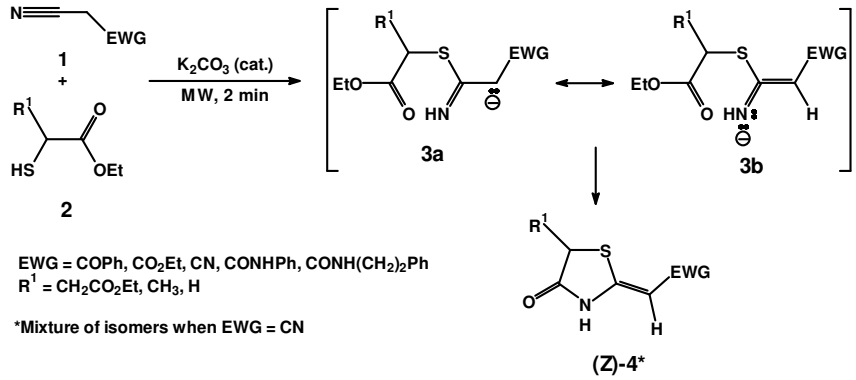
report the first dry-media microwave synthesis of β-enamino-type (Z)-4-oxothiazolidine derivatives **4**[20,21], from activated nitriles **1** and α-mercapto-esters **2** (**Scheme-I**). Literature search indicated that only two examples of microwave synthesis of the heterocyclic compounds possessing the exocyclic C=C bond, *i.e.*, 4-alkylidene-1*H*-imidazol-5(4*H*)-ones[22] and 2-phenyl-4-arylidene-5(4*H*)-oxazolones[4] have been reported so far.



Scheme-I

EXPERIMENTAL

General procedures: Typical experimental procedure for the reactions carried out in a CEM Focused Microwave Synthesizer (Method **A**): thoroughly mixed neat nitrile **1** (1 mmol), mercapto reactant **2** (1.1 mmol) and potassium carbonate (2 % mol equivalent) were placed in a glass vial containing a small stirring bar. The glass vial was sealed and exposed to microwaves (150 W) at 80 ºC for 2 min. After cooling to room temperature, the progress of the reaction was checked by TLC. In two cases during the unsatisfactory synthesis of **4b** and **4c**, as indicated by the presence of appreciable amounts of reactants, the reaction mixture was irradiated again for another 2 min, however without result in terms of better yields. In all other cases the reaction mixture was dissolved in an appropriate solvent (ethyl acetate, ethanol or acetonitrile) filtered and concentrated to a small volume. The resulting viscous residue or suspension was chromatographed on silica (toluene/ethyl acetate gradient) affording the final product **4** as white crystals. As in the case of 2-alkylidene-4-oxothiazolidines **4a-b** and **4d-l**, previously synthesized by conventional method[21], the structural assignments of new compounds **4c**, **4m** and **4n** were made on the basis of spectroscopic data (IR, ^{1}H and ^{13}C NMR, MS, UV) and elemental analysis. Analytically pure samples were obtained by crystallization from ethanol.

(Z)-(5-Methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (4c): m.p. 209-211 °C; IR ($CHCl_3$, cm^{-1}) 3254, 3082, 1708, 1627, 1598, 1576, 1522, 1453, 1370, 1309, 1250, 1181, 813, 780, 748 and 698; ^1H NMR (200 MHz; DMSO-d_6) 1.50 (3 H d, J = 7.2, CH_3), 4.08 (1 H, q, J 7.2, CHS), 6.80 (1 H, s, =CH), 7.48-7.63 (3 H, m, *m*- and *p*-phenyl), 7.83-7.87 (2 H, m, *o*-phenyl), 11.80 (1 H, s, NH); ^{13}C NMR (50 MHz; DMSO-d_6) 18.3 (CH_3), 41.0 (CHS), 94.5 (=CH), 127.3 (*o*-phenyl), 129.0 (*m*-phenyl), 132.3 (*p*-phenyl), 138.5 (C1-phenyl), 160.6 (C=), 177.7 (CO_{ring}), 187.5 (CO_{ketone}); MS m/z: 234 (M + 1); UV λ_{max} (DMSO)/nm 335 (ε/dm^3 mol^{-1} cm^{-1} 23 300); Anal. Calcd. (%) for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00; S, 13.75; Found: C, 61.60; H, 4.70; N, 6.03; S, 13.97.

(Z)-(4-Oxothiazolidin-2-ylidene)-N-(2-phenylethyl)ethanamide (4m): m.p. 205-206 °C; IR ($CHCl_3$, cm^{-1}) 3312, 3166, 3055, 1699, 1640, 1565, 1497, 1463, 1311, 1267, 1184, 886, 818, 787, 729 and 692; ^1H NMR (200 MHz; DMSO-d_6) 2.71 (2 H, t, J = 7.3, CH_2Ph), 3.25-3.35 (2 H, m, NCH_2), 3.63 (2 H, s, CH_2S), 5.59 (1 H, s, =CH), 7.15-7.33 (5 H, m, Ph), 7.83 (1 H, t, J 5.4, NH_{amide}), 11.27 (1 H, s, NH_{ring}); ^{13}C NMR (50 MHz; DMSO-d_6) 32.1 (CH_2S), 35.7 (CH_2Ph), 40.3 (NCH_2), 92.7 (=CH), 126.3 (*p*-phenyl), 128.6 (*o*-phenyl), 128.9 (*m*-phenyl), 139.9 (C1-phenyl), 151.9 (C=), 166.8 (CO_{amide}), 174.3 (CO_{ring}); MS m/z: 263 (M + 1); UV λ_{max} (DMSO)/nm 283 (ε/dm^3 mol^{-1} cm^{-1} 23 150); Anal. Calcd. (%) for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22; Found: C, 59.47; H, 5.38; N, 10.61; S, 12.51.

(Z)-(5-Methyl-4-oxothiazolidin-2-ylidene)-N-(2-phenylethyl)-ethanamide (4n): m.p. 195 °C; IR ($CHCl_3$, cm^{-1}) 3295, 3084, 3054, 1702, 1644, 1576, 1499, 1456, 1374, 1314, 1275, 1184, 823, 786, 735 and 699; ^1H NMR (200 MHz; DMSO-d_6) 1.41 (3 H, d, J = 7.2, CH_3), 2.71 (2 H, t, J = 7.3, CH_2Ph), 3.24-3.35 (2 H, m, CH_2N), 3.89 (1 H, q, J = 7.2, CHS), 5.57 (1 H, s, =CH), 7.16-7.33 (5 H, m, Ph), 7.84 (1 H, t, J 5.4, NH_{amide}), 11.23 (1 H, br s, NH_{ring}); ^{13}C NMR (50 MHz; DMSO-d_6) 19.0 (CH_3), 35.6 (CH_2Ph), 40.3 (NCH_2), 40.6 (CHS), 92.7 (=CH), 126.2 (*p*-phenyl), 128.5 (*o*-phenyl), 128.8 (*m*-phenyl), 139.9 (C1-phenyl), 150.0 (C=), 166.6 (CO_{amide}), 176.9 (CO_{ring}); MS m/z: 277 (M + 1); UV λ_{max} (DMSO)/nm 284 (ε/dm^3 mol^{-1} cm^{-1} 27 200); Anal. Calcd. (%) for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; S, 11.60; Found: C, 60.54; H, 5.83; N, 10.11; S, 11.69.

RESULTS AND DISCUSSION

The comparative results, regarding the conventional preparation[21] and microwave-assisted syntheses of **4**, using a focused single-mode microwave reactor (Method **A**) and domestic microwave unit (Method **B**), are summarized in Table-1.

TABLE-1
SYNTHESIS OF 4-OXOTHIAZOLIDINES **4** BY CONVENTIONAL METHOD AND UNDER MICROWAVE (MW) IRRADIATION

Entry	Products	EWG	R^1	Yield (%)[a]		
				Conventional method[b]	MW method **A**[c]	MW method **B**[d]
1	**4a**	COPh	CH_2CO_2Et	68	59	65
2	**4b**	COPh	H	79	20	51
3	**4c**	COPh	CH_3	63	10	10
4	**4d**	CO_2Et	CH_2CO_2Et	62	86	72
5	**4e**	CO_2Et	H	67	95	54
6	**4f**	CO_2Et	CH_3	59	69	87
7	**4g**	CN	CH_2CO_2Et	68	88	87
8	**4h**	CN	H	68	88	83
9	**4i**	CN	CH_3	75	78	99
10	**4j**	CONHPh	CH_2CO_2Et	77	49	39
11	**4k**	CONHPh	H	97	66	92
12	**4l**	$CONH(CH_2)_2Ph$	CH_2CO_2Et	60	63	88
13	**4m**	$CONH(CH_2)_2Ph$	H	83	86	55
14	**4n**	$CONH(CH_2)_2Ph$	CH_3	80	66	81

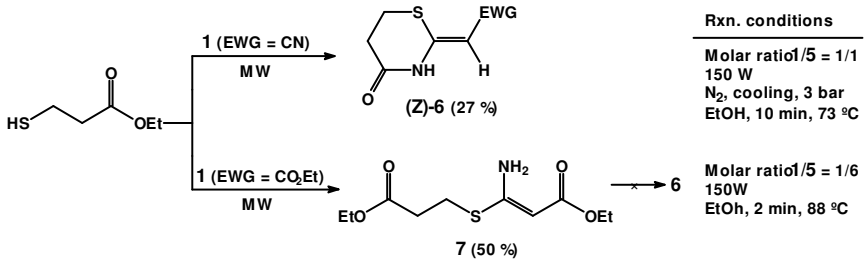
[a]Products purified by chromatography; the spectroscopic data of compounds **4a-b** and **4d-l** were identical with these of the authentic samples prepared previously by conventional method[21].
[b]Rxn. time: 2-9 h; molar ratio **1/2** = 1/1 to 1/1.7; solvent: EtOH; catalyst: K_2CO_3.
[c]Method **A**: Single mode MW irradiation at 80 ºC and 150 W power for 2 min; molar ratio **1/2** = 1/1.1.
[d]Method **B**: MW irradiation applying 50-100 % of the maximum power (750 W), for 10-150 s; in some cases sequential irradiations (30 s each) were applied for the total time (150 s).

The present investigation began by examining a wide variety of reaction conditions for focused MW-mediated reactions of neat nitriles **1** (entries 4-6) with 1.1 molar equivalent of diethyl α-mercaptobutandioate in the presence of a catalytic amount of potassium carbonate. Ultimately, upon controlled irradiation of the reaction mixture at 80 °C and 150 W (Method **A**), almost complete consumption of the reactants was indicated after 2 min (TLC). Yields of isolated, chromatographically purified products **4d-f** were quite good (69-95 %) and better than these of the conventional method. Moreover, preliminary reactions (entries 8 and 9) carried out in the unmodified domestic oven, applying 50 % of the maximum power of 750 W (Method **B**), afforded after only 10 s, the desired 4-oxothiazolidines **4h** and **4i** in high yields, practically without side products.

The multiple rate enhancement reflects obviously the faster heating of the reaction mixture due to the increased microwave power. However, in terms of the polar mechanism (**Scheme-I**), the stereoselective synthesis of (Z)-4-oxothiazolidine derivatives **4** is thought to be a perfect case for the observation of the specific MW effect[1-3]. Namely, based on calculations using the MNDO-PM3 method, it has been established that in the conventional synthesis of (Z)-4-oxothiazolidine derivatives **4** the ring-formation (step **3**→**4**) occurs *via* the anionic intermediate **3**[23]. As a consequence, the polarity of the system increases during the reaction course from reactants **1** and **2** to the more stabilized transition state, that structurally resembles the anionic species **3**. Therefore, an expected decrease in the activation energy of the MW-initiated reactions, correlates with the strong rate acceleration. The two-step one-pot reaction (**Scheme-I**), proceeded under precise temperature and power settings with a diverse range of reactants **1** and **2**, indicating the generality of the method **A**. In the case of 4-oxothiazolidines **4j-n**, reactions took place at the temperature well below the melting points of the starting nitriles **1**[21,24]. Synthesis of compounds **4** in the house microwave oven occurred with equal facility (Table-1; last column). All of the above examples, unlike the classical method, refer to the solvent-free synthesis of 4-oxo-thiazolidines **4**[25-28] without solid support. In contrast to the accelerated MW synthesis, the conventional one, which does not proceed without solvent, requires, under the optimized conditions, drastically longer reaction times (2-9 h) and the use of a larger molar excess of the mercapto reactant **2** relative to nitrile **1** (Table-1, column V). As can be seen, only MW-assisted reaction of **1** (EWG = COPh) and **2** ($R^2 = CH_3$) did not effectively proceed under the usual reaction conditions, **4c** being formed in low 10 % yield. In both cases, in addition to the products **4b** and **4c**, the corresponding reactants were recovered. Interestingly, the cyclized product **4b** was produced in a satisfactory yield (50 %) using the domestic MW unit (Method **B**), but under the focused irradiation (Method **A**) the yield was only 20 %.

In all conventional syntheses, as established in earlier studies[21] and in syntheses under the influence of microwaves as well, the products **4** were isolated as the single (Z)-isomers. An exception refers to the Z,E-mixtures in the case of 4-oxothiazolidines **4**, containing the nitrile group attached to the exocyclic C=C bond (entries 7-9). In addition, the heterocyclization step, occurring through *in situ* formed intermediate **3** (with EWG = CH_2CO_2Et), proceeded in a regiospecific manner to give only 2-alkylidene-4-oxothiazolidines. An alternative mode of intramolecular cyclization, leading to the concurrent six-membered ring 4-oxo-1,3-thiazinane derivatives, was not observed.

Noteworthy in this context is the possibility to carry out time-controlled microwave synthesis of thiazinane-type products **6**[20] with the β-mercapto-substituted substrates and nitriles **1** (**Scheme-II**). For instance, when malononitrile was reacted with an equimolar amount of 3-mercapto-propanoate with 5 mol % of K_2CO_3 as a catalyst in ethanol, under focused microwave irradiation for 10 min, the corresponding 2-(4-oxo-1,3-thiazinan-2-ylidene)acetonitrile (**6**; EWG = CN) was obtained in 27 % yield. In sharp contrast, the reaction of **5** with ethyl cyanoacetate under the thermal heating in ethanol solution led to a complex mixture, whereas the expected product **6** (EWG = CO_2Et) was isolated in negligible yield (3 %).



Scheme-II

Furthermore, shorter microwave exposure of the same reaction mixture (2 min), in the presence of the large excess of the reactant **5** (**Scheme-II**), yielded in moderate yield the addition product, ethyl 3-amino-3-(2-ethoxy-carbonylethylsulfanyl)propenoate (**7**), that is the intermediate leading to ethyl (4-oxo-1,3-thiazinan-2-ylidene)ethanoate (**6**; EWG = CO_2Et). Under the reaction conditions employed, the heterocycle **6** was not detected even in minute quantities. The lack of cyclization of **7** into the cyclic compound **6** can be adequately explained by taking into account the stability of **7** due to the formation of intramolecular hydrogen bond between the proximal amino and ester groups. However, the isolation of **7** under these reaction conditions is another comparative advantage of the microwave-controlled reaction. This indicates that MW procedure could be adaptable to a wide range of similar processes giving rise to heterocyclic compounds of synthetic and biological interest.

In summary, the feasibility of regio- and stereoselective MW-induced synthesis of a series of (Z)-2-alkylidene-4-oxothiazolidines from activated β-oxonitriles **1** and α-mercaptoesters **2** has been demonstrated. In comparison to classical synthesis, the method is simpler, faster and environmentally cleaner, as no organic solvent and/or solid support have been employed during the reaction course.

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