One-pot Three Component Synthesis of ω-(oxathiolan-2-thion-5-yl)-α-oxazolidin-2-ones

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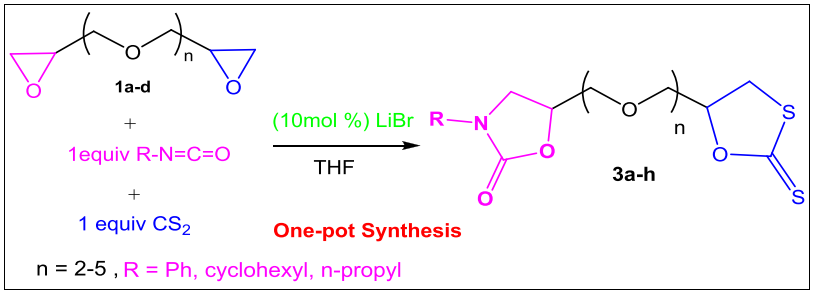
Additional Supporting Information may be found in the online version of this article.
Received May 21, 2016
DOI 10.1002/jhet.2834
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).



We report a practical and one-pot synthesis of novel series of ω-(oxathiolan-2-thione-5-yl)-α- oxazolidin-2-ones (**3a-h**). The obtained compounds have been designed, synthesized via reaction of oligoethylene glycols diglycidyl ethers, isocyanate and carbon disulfide in the presence of catalytic amount of lithium bromide. A variety of important oxazolidinone derivatives can be obtained from simple starting materials in good yields and the biological activity of these new products will be investigated in complementary study.

INTRODUCTION

Multicomponent reactions (MCRs) provide unmatched opportunities for the expeditious increase of complexity and diversity in synthetic outcomes. This approach allows developing more complex molecular structures from simple and available reagents via a transformation with single step and does not require the isolation of intermediates products [1]. MCRs have been one of the best approaches that meet the requirements of green chemistry as well as the library development of medicinal compounds [2].

Oxazolidinones are well-known five-membered nitrogen and oxygen-containing compounds. These have been reported to possess biological activities such as antibacterial activity [3]. This new class of synthetic antibacterial agents exhibit activity against a large number of Gram-positive organisms. Many oxazolidinone derivatives are in clinical use such as Linezolid [4] and Dup-721 [5] and are two important examples of drugs that contain the 2-oxazolidinone ring. Of the totally synthetic antibiotics, Dup-721 was the first drug candidate of this family, whereas linezolid was the first member of this series introduced in the market (known as Zyvox).

Oxazolidinones [6] are heterocyclic compounds that play an essential role in the synthesis of several organic molecules, covering amino acids [7], amino alcohols [8], amides [9], peptides [10], and polyfunctional compounds [11]. Some natural and synthetic derivatives oxazolidinone have important biological activities such as anticancer [12], antibacterial [13], anti-inflammatory [14], anticonvulsant [15], antituberculosis [16], anti-VIH [17], and antidiabetic [18]. The oxazolidinones are also necessary for the development of drugs, especially inhibitors of monoamine oxidase [19].

On the other hand, five-membered cyclic dithiocarbonates have received much attention in view of their biological activity and material science [20]. An efficient method for synthesizing cyclic dithiocarbonates is performed by the coupling reaction of carbon disulfide with epoxides [21]. Much attention has been paid to sulfur-containing polymers [22]. These polymers have superior optical and thermal properties [23–29] and are, therefore, expected to be useful as optical lenses and fibers. The cycloaddition of isocyanates with epoxides is one of the most useful and efficient method for preparation of oxazolidin-2-ones. A variety of catalysts have been investigated, such as quaternary ammonium salts [24], LiBr/n-Bu_3PO or LiBr/HMPA [25], LiCl/DMF [26], n-Bu_3SnI-Ph_3PO [27], n-Bu_3SnI-Ph_4-SbI [28], and lanthanide chlorides [29]. Other catalysts are recently introduced into the synthesis of oxazolidinones particularly MgI_2 etherate [30], complex rare-earth-metal

[31], Brønsted base [32], aluminum [33], bimetallic aluminum (salen) [34], vanadium V(Salen) [35], Pd [36], and titanium (salen) [37]. It has recently been reported that the reaction of epoxides and carbon disulfide is known to lead to a range of products including 1,3-oxathiolane-2-thione. In recent decades, many catalyst systems, including amines, alkali metal salts and quaternary ammonium salts, potassium alcoholates, and transition metal complexes, have been developed for this transformation [38–43].

In continuation of our efforts toward the development of novel methodologies for the synthesis of heterocyclic compounds, gathering the two patterns in one molecule and combining their properties was our purpose and presents a new way to increase the efficiency of biologically active molecules. Herein, we designed a new synthetic route to novel hybrid molecules containing 3,5-disubtitued oxazolidin-*2*-one and oxathiolan-*2*-thione moiety.

RESULTS AND DISCUSSION

Two steps synthesis of ω-(oxathiolan-2-thione-5-yl)-α-oxazolidin-2-ones. In a previous work, we reported the synthesis of symmetrical bis-oxazolidinone [44] bridged with a polyoxyethylene chain via reaction of oligoethylene glycols diglycidyl ethers with simple isocyanate in the presence of catalytic amount of lithium bromide. In this context, we have described also in earlier paper the synthesis of symmetrical bis(cyclic dithiocarbonate) [45] from the same diglycidyl ethers and carbon disulfide with the same catalyst.

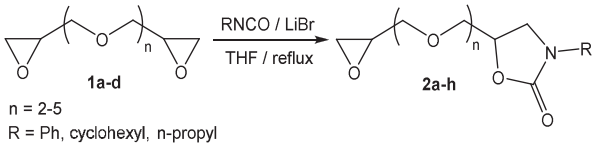
Our approach started with the synthesis of oligoethylene glycols diglycidyl ethers [46] **1a–d** from commercially accessible epichlorohydrin and polyoxyethylene glycols following a literature conditions under phase-transfer catalysis in basic medium. When treated with one equivalent of various simple isocyanates in boiling anhydrous THF in the presence of catalytic amount of lithium bromide, oligoethylene glycols diglycidyl ethers **1** afforded a corresponding epoxyoxazolidin-*2*-one of polyoxyethylene **2a–h** at 54%–87% yield after purification with flash column chromatography (Table 1).

It is worth to note that the reaction of diglycidyl ethers 1 with one equivalent of simple isocyanate leads exclusively to the epoxyoxazolidin-2-one **2**. The absence of the bis-oxaoxazolidinone could be interpreted on the basis that the two sides of the chain are far enough separated from each other that they would react as one unit and all diepoxide react similarly, and thus, the cycloaddition of isocyanate occurs in the same time and the same probability with one oxirane ring giving unsymmetrical epoxyoxazolidinone (Table 2).

In the second step, the use of one equivalent of carbon disulfide in anhydrous dichlromethane under reflux in the presence of the same catalyst lithium bromide, the epoxyoxazolidinones **2** was converted into the corresponding ω-(oxathiolan-*2*-thione-5-yl)-α-oxazolidin-*2*-ones **3** in 60%–86% yields after purification with column chromatography (Table 3). The choice of dichloromethane, in this case, is dictated to avoid the formation of undesired secondary products at higher temperature such as cyclic trithiocarbonate. The elevation of temperature engendered lower yields of products **3**, and it may contribute to the volatility of molecular carbon disulfide.

Table 1

Optimization reaction conditions[a] synthesis of epoxyoxazolidinone **2**.



Entry	n	R	Epoxyoxazolidine **2**	Reaction Time (h)[b]	Yield (%)[c]
1	2	Ph-	2a	6	54
2	3	Ph-	2b	8	68
3	4	Ph-	2c	12	76
4	5	Ph-	2d	16	87
5	3	cyclohexyl	2e	12	65
6	4	cyclohexyl	2f	15	73
7	3	n-propyl	2 g	12	60
8	4	n-propyl	2 h	15	68

[a]Reaction conditions: 1 (3 mmol, 1equiv) in 15 mL anhydrous THF; 0,3 mmol lithium bromide, isocyanate (3 mmol, 1equiv) in 5 mL anhydrous THF, N_2.
[b]Reaction time is determined by TLC (eluent: Acetone/Ether: 20/80).
[c]Yields is determined after purification with flash column chromatography.

Table 2

Scope of epoxyoxazolidinone **2**.

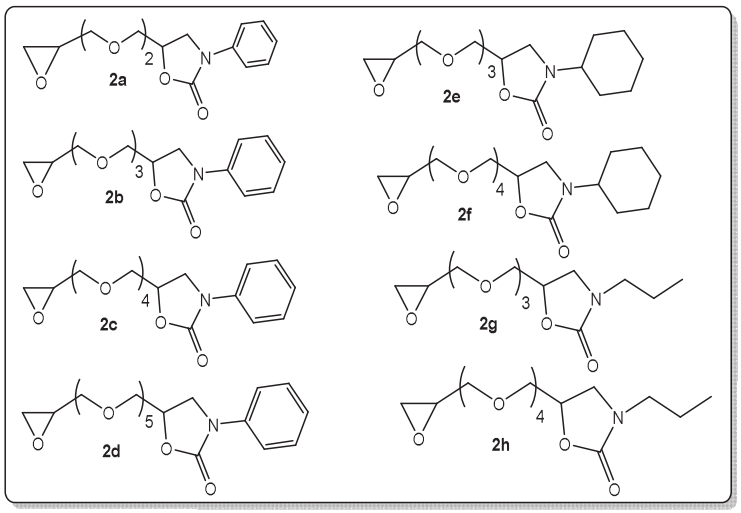
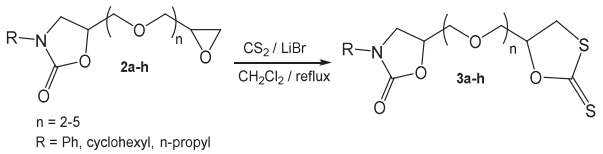


Table 3

Reaction conditions[a] synthesis of compounds 3 from epoxyoxazolidinone.



Entry	n	R	Product 3	Reaction Time (h)[b]	Yield (%)[c]
1	2	Ph-	3a	3	60
2	3	Ph-	3b	5	68
3	4	Ph-	3c	8	76
4	5	Ph-	3d	10	86
5	3	cyclohexyl	3e	6	64
6	4	cyclohexyl	3f	9	71
7	3	n-propyl	3 g	8	57
8	4	n-propyl	3 h	10	62

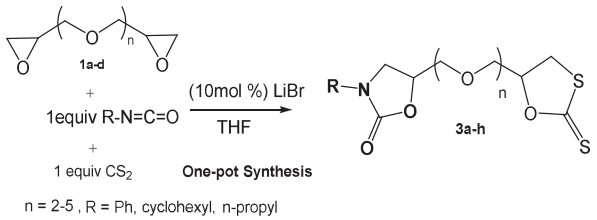
[a]Reaction conditions: 1 (1 mmol, 1equiv) in 15 mL anhydrous THF; 0,1 mmol lithium bromide, carbon disulfide (1 mmol, 1equiv) in 5 mL anhydrous THF, N_2.
[b]Reacttion time is determined by TLC (eluent: Acetone/Ether: 40/60).
[c]Yields is determined after purification with column chromatography.

So the optimum temperature is 35°C to obtain highest yields of desired products with a short reaction time (Table 3).

One-pot three-component synthesis of target compounds 3a–d. To further improve this method, with the optimized conditions established previously, we decided to probe the generality of this MCR that performed in one pot from three components. Thus we have developed a series of ω-(oxathiolan-2-thione-5-yl)-α-oxazolidin-2-ones polyoxyethylene **3a–h**, by reacting in anhydrous THF the diglycidyl ethers **1a–d** with one equivalent of simple isocyanate and one equivalent of carbon disulfide in the presence of catalytic amount of lithium bromide. A variety of simple isocyanate, such as phenylisocyanate, propylisocyanate, and cyclohexylisocyanate were tested (Table 4). The results obtained are reported in Table 5. The results clearly show that all reactions proceeded smoothly to afford the expected compounds **3a–h** in good yields. The reaction started by refluxing in anhydrous THF under nitrogen atmosphere, 1 mmol of

Table 4

Multicomponent reaction conditions[a] synthesis of substrate **3**.

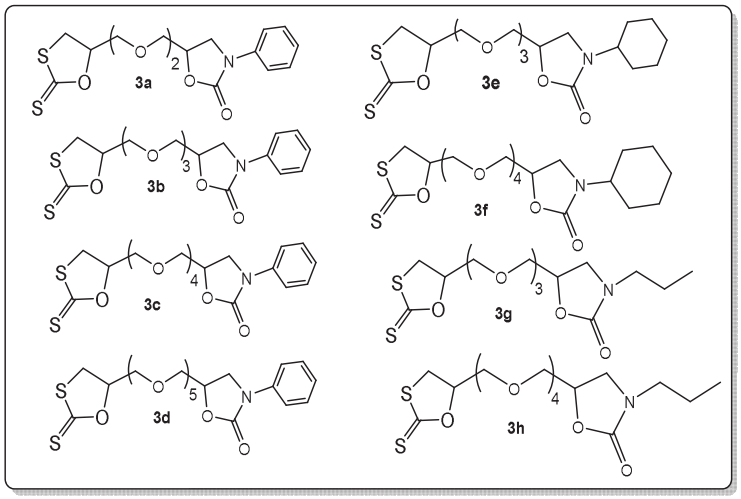


Entry	n	R	Product **3**	Reaction Time (h)[b]	Yield (%)[c]
1	2	Ph-	3a	7	67
2	3	Ph-	3b	10	73
3	4	Ph-	3c	14	80
4	5	Ph-	3d	18	89
5	3	cyclohexyl	3e	13	70
6	4	cyclohexyl	3f	16	75
7	3	n-propyl	3 g	15	60
8	4	n-propyl	3 h	19	67

[a]Reaction conditions: 1 (1 mmol, 1equiv) in 15 mL anhydrous THF; 0,1 mmol lithium bromide, isocyanate (1 mmol, 1equiv) in 5 mL anhydrous THF; isocyanate (1 mmol, 1equiv) in 5 mL anhydrous THF, N_2.
[b]Reaction time is determined by TLC (eluent: Acetone/Ether: 40/60).
[c]Yields is determined after purification with column chromatography.

Table 5

Scope of substrate **3**.

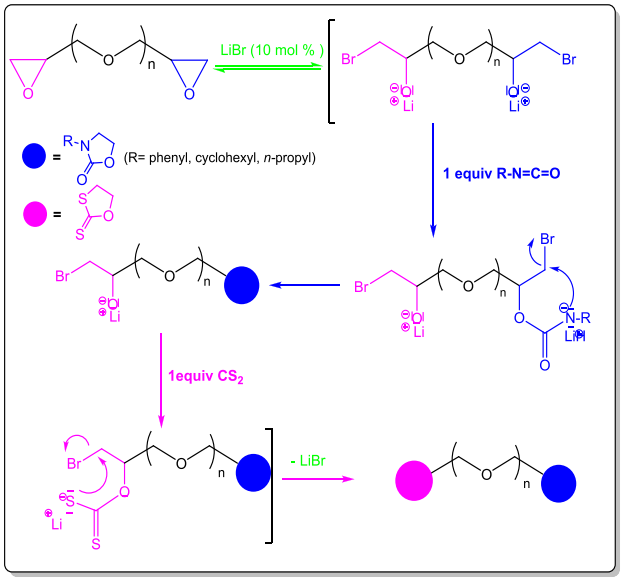


diepoxydes **1a–d** and 0.1 mmol of lithium bromide for 30 min and then 1.1 mmol of simple isocyanate was added and left under reflux. After the consummation of totally amount of isocyanate monitored by TLC (acetone/ether: 40/60), the mixture was cooled at room temperature, and 1.1 mmol of carbon disulfide was also added, and the reaction was left to stand at room temperature (Table 5).

Operationally, the reaction allows economizing the catalytic amount of lithium bromide, solvent, and reduces also the reaction time. Concerning yields, MCR provides much better yields, because it avoids the isolation and minimizes losses during purification process of the intermediate product **2a–h**.

As depicted in Scheme 1, the plausible mechanism reaction started by the condensation of diglycidyl ethers

Scheme 1. Proposed mechanism for synthesis of ω-(oxathiolan-2-thione-5-yl)-α-oxazolidin-2-ones **3**. [Color figure can be viewed at wileyonlinelibrary.com]



and lithium bromide lead to secondary bromohydrin salts (bis-oxiranes and LiBr are mixed and left for 30 min) via nucleophilic attack at terminal carbon of the oxirane ring. The secondary bromohydrin salt reacts with simple isocyanate to yield the corresponding carbamate followed by intramolecular ring closure for epoxyoxazolidin-2-ones **2**. When carbon disulfide was added, the second site of bromohydrin salt reacts to give the thiolate ion, which undergoes a cyclization reaction to give the oxathiolane ring.

All new compounds of epoxyoxazolidinone **2** nand ω-(oxathiolan-2-thione-5-yl)-α-oxazolidin-*2*-ones **3** were fully characterized by spectroscopic data of ^{1}H and ^{13}C NMR, FTIR, and high-resolution mass spectra (HRMS). For example, the ^{1}H NMR spectra of target compound **2c** showed the presence of double doublet about 2.53–2.56 ppm related to the first proton of methylene epoxide ring. The second proton of methylene oxirane ring resonates as a double doublet at 2.71–2.73 ppm. The single proton linked to epoxide ring appears as a multiplet centered at 3.10 ppm. The formation of target compounds **2c** was confirmed also by the presence of a new multiplet at 3.82–4.02 ppm attributed to protons of methylene CH_2N-C = O moiety of oxazolidinone ring and another multiplet in the range of 4.66–4.73 ppm related to proton connected to oxazolidinone ring. The ^{13}C NMR of compound **2c** exhibited principally for C = O group a singlet at 154.6 ppm and another singlet at 47.0 ppm assigned to the methylene carbon of the CH_2N-C = O moiety.

It is worth to note that the reaction of diglycidyl ethers **1** with one equivalent of simple isocyanate leads exclusively to the epoxyoxazolidin-2-one **2**. The symmetrical bis-oxazolidinone is not observed in this case this is confirmed with ^{1}H and ^{13}C NMR data. The non-doubling of signals relating to the proton of oxazolidinone and methylene protons of the CH_2-NCO groups in both spectra of crude and purified product is in favor that the bis-oxazolidinone is not observed in our case. The ^{13}C NMR confirms also the absence of bis-oxazolidinone via the non-doubling of signals relating to the carbon of CO and CH_2-NCO groups.

For instance, the ^{1}H NMR spectra of compound **3c** showed the absence of signals related to oxirane protons (2.5–3.2 ppm) and the apparition of new multiplet in the range 5.13–5.24 ppm assigned to the cyclic proton of oxathiolan-*2*-thione group and another multiplet at 3.81–3.87 ppm due to the CH_2 protons of the CH_2-S-C = S moiety. The signals of cyclic proton of oxazolidinone group appears as a multiplet at a range of 4.68–4.75 ppm and another multiplet at 3.92–4.23 ppm due to the CH_2 protons of the CH_2-N-C = O moiety. Interestingly, the ^{13}C NMR spectra of compound 2 exhibited for C = S group a signal at 212.4 and 154.5 ppm for C = O group.

CONCLUSION

We have developed a highly efficient method for the synthesis of ω-(oxathiolan-2-thione-5-yl)-α-oxazolidin-2-ones bridged by a polyoxyethylene chain from oligoethylene glycols diglycidyl ethers, simple isocyanates, and carbon disulfide via LiBr-catalyzed MCRs. The notable advantages of this method are mild reaction conditions, short reaction time, good yields, and an expedient atom-economic approach to the synthesis of target compounds **3** from readily available raw materials: small amounts of nontoxic LiBr as catalyst and low amounts of solvents. In addition to operational simplicity, there is no need to isolate and purify the intermediate product. This practical protocol presents a simple direct route to access a new important unsymmetrical structure containing two biological oxathiolane-2-thione and oxazolidinone groups.

EXPERIMENTAL

The IR spectra were performed on SHIMADZU JASCO FTIR 4000/6000 SERIES. The ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AC-300 at 300 and 75 MHz, respectively. All spectra were obtained using $CDCl_3$ as solvent and referenced to TMS. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Coupling constant in hertz (Hz). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale.

HRMS were obtained from FINIGAN MAT 95. Columns chromatography was performed using silica gel (Fluka 40–60 μm). Analytical TLC was performed using Silica Gel 60 F254 plates (Fluka 40–60 μm). The developed chromatogram was visualized under UV lamp (254 nm). All commercially available reagents were used without further purification. Anhydrous THF was distilled from sodium. All reactions were carried out under a protective atmosphere of dry nitrogen using oven-dried glassware unless otherwise stated.

General procedure for preparation of epoxyoxazolidinone 2a–h. The reaction was carried out under a nitrogen atmosphere. The solution of oligoethylene glycols diglycidyl ether **1a–d** (3 mmol) in 10 mL of anhydrous THF was added to lithium bromide (0.3 mmol, 0.026 g). After stirring the mixture at reflux for 0.5 h, a solution of isocyanate (3.3 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 6–16 h (see Table 1). The progress of the reaction was monitored with TLC (Acetone/Ether: 20/80). At the end of the reaction, the mixture was cooled, diluted with water (40 mL), and then extracted with dichloromethane (4 × 40 mL). It was washed with water (2 × 30 mL) and dried on anhydrous $MgSO_4$. The solvent was removed, and the residue was purified on column chromatography (eluent: Acetone /Ether: 80/20) to obtain the epoxyoxazolidinones **2a–h** as viscous oils.

5-(6-oxiran-2,5-dioxahexan-5-yl)-3-phenyl oxazolidin-2-one (2a). Colorless viscous oil, 512 mg, 54% yield. IR ($CHCl_3$) 1758 (C = O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41–2.46 (dd, 1H), 2.61–2.66 (dd, 1H), 2.98–3.07 (m, 1H), 3.21–3.37 (m, 2H), 3.42–3.70 (m, 6H), 3.75–4.00 (m, 2H), 4.50–4.61 (m, 1H), 7.00–7.63 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.2, 46.8, 50.7, 69.6, 70.6 (m, 2C); 71.23, 71.94, 118.02 (m, 2C), 123.81, 128.7 (m, 2C), 138.2, 154.6. HRMS (ESI) calcd for $C_{15}H_{19}NO_5Na$ $[M + Na]^+$ 316.1161, found 316.1159.

5-(9-oxiran-2,5,8-trioxanonan-5-yl)-3-phenyloxazolidin-2-one (2b). Colorless viscous oil, 734 mg, 68% yield. IR ($CHCl_3$) 1739 (C = O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45–2.53 (dd, 1H), 2.68–2.72 (dd, 1H), 3.05–3.09 (m, 1H), 3.26–3.43 (m, 2H), 3.50–3.70 (m, 10H), 3.80–3.89 (m, 1H), 3.91–4.02 (m, 1H), 4.64–4.76 (m, 1H), 6.90–7.50 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.2, 46.9, 50.9; 69.4, 70.5 (m, 4C), 71.3, 71.9, 118.2, 118.6, 123.1, 128.9, 128.9, 138.2, 154.8. HRMS (ESI) calcd for $C_{17}H_{23}NO_6Na$ $[M + Na]^+$ 360.1423, found: 360.1425.

5-(12-oxiran-2,5,8,11-tetraoxadodecan-5-yl)-3-phenyloxazolidin-2-one (2c). Colorless viscous oil, 921 mg, 76% yield. IR ($CHCl_3$) 1760 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.53–2.56 (dd, 1H), 2.71–2.73 (dd, 1H), 3.08–3.12 (m, 1H), 3.29–3.44 (m, 2H), 3.49–3.78 (m, 14H), 3.82–3.89 (m, 1H), 3.94–4.02 (m, 1H), 4.66–4.73 (m, 1H), 7.05–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 44.1, 47.0, 50.7, 69.8, 70.5 (m, 6C), 71.2, 71.9, 118.1 (s, 2C), 123.8, 128.9 (m, 2C), 138.2, 154.6. HRMS (ESI) calcd for $C_{19}H_{27}NO_7Na$ $[M + Na]^+$ 404.1685, found 404.1686.

5-(15-oxiran-2,5,8,11,14-pentaoxatetrade can-5-yl)-3-pheny loxazolidin-2-one (2d). Colorless viscous oil, 1169 mg, 87% yield. IR ($CHCl_3$) 1761 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.55–2.62 (dd, 1H), 2.72–2.79 (dd, 1H), 3.12–3.17 (m, 1H), 3.31–3.42 (m, 2H), 3.45–3.70 (m, 18H), 3.81–3.92 (m, 1H), 3.96–4.08 (m, 1H), 4.72–4.81 (m, 1H), 7.06–7.58 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.0, 46.8, 50.6, 69.6, 70.5 (m, 8C), 70.96, 71.22, 117.9 (m, 2C), 123.7, 128.9 (m, 2C), 138.2, 154.5. HRMS (ESI) calcd for $C_{21}H_{31}NO_8Na$ $[M + Na]^+$ 448.1947, Found 448.1948.

5-(9-oxiran-2,5,8-trioxanonan-5-yl)-3-cyclohexyloxazolidin-2-one (2e). Colorless viscous oil, 659 mg, 65% yield. IR ($CHCl_3$) 1721 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82–1.07 (m, 5H), 1.30–1.64 (m, 5H), 2.32–2.35 (dd, 1H, ^2J = 6.0, ^3J = 3.0 Hz), 2.50–2.53 (dd, 1H, ^2J = 4.5, ^3J = 3.0 Hz), 2.87–2.90 (m, 1H), 3.09–3.12 (m, 1H), 3.13–3.16 (m, 2H), 3.37–3.39 (m, 8H), 3.51 (dd, 1H), 3.54–3.55 (dd, 1H), 3.88–3.89 (m, 2H), 4.59–4.60 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1 (s, 2C), 25.6, 33.6 (s, 2C), 43.7, 49.5, 50.5, 63.2, 69,5, 70,1 (m, 4C), 71.1, 156.8. HRMS (ESI) calcd for $C_{16}H_{29}O_5NNa$ $[M + Na]^+$ 338.1943, found 338.1945.

5-(12-oxiran-2,5,8,11-tetraoxadodecan-5-yl)-3-cyclohexyl oxazolidin-2-one (2f). Colorless viscous oil, 837 mg, 73% yield. IR ($CHCl_3$) 1724 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.02–1.73 (m, 10H), 2.54–2.56 (dd, 1H), 2.71–2.74 (dd, 1H), 3.07–3.13 (m, 1H), 3.31–3.33 (m, 1H), 3.35–3.38 (m, 2H), 3.57 (m, 12H), 3.71–3.73 (dd, 1H), 3.75–3.77 (dd, 1H), 4.00–4.07 (m, 2H), 4.51–4.58 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2 (s, 2C), 30.0, 30.2 (s, 2C), 42.5, 44.1, 50.7, 52.3, 70.3, 70.2 (m, 4C), 71.6 (s, 1C), 157.0. HRMS (ESI): *m/z* [M + Na] calcd for $C_{18}H_{33}O_6NNa$ 382.2206, Found 382.2207.

5-(9-oxiran-2,5,8-trioxanonan-5-yl)-3-propyl oxazolidin-2-one (2g). Colorless viscous oil, 536 mg, 60% yield. IR ($CHCl_3$) 1750 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.74–0.79 (m, 3H), 1.34–1.41 (m, 2H), 2.47–2.49(dd, 1H), 2.62–2.67 (dd, 1H), 2.94–2.98 (m, 1H), 3.01–3.04 (dt, 2H), 3.24–3.26 (dd, 1H), 3.27–3.31 (dd, 1H), 3.53 (m, 8H), 3.65–3.66 (dd, 1H), 3.68–3.70 (dd, 1H), 4.04–4.07 (dd, 2H), 5.17–5.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 22.8, 42.5, 45.4, 50.6, 63.5, 69.4, 70.3, 70.5 (m, 4C), 71.8, 157.8. HRMS (ESI) calcd for $C_{13}H_{25}O_5NNa$ $[M + Na]^+$ 298.1630, found: 298.1633.

5-(12-oxiran-2,5,8,11-tetraoxadodecan-yl)-3-propyl oxazolidin-2-one (2h). Colorless viscous oil, 698 *mg*, yield: 68%. IR ($CHCl_3$) 1727.50 (C = O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.83–0.91 (m, 3H), 1.39–1.48 (m, 2H), 2.44–2.48 (dd, 1H), 2.58–2.62 (dd, 1H), 2.83–2.89 (m, 1H), 3.05–3.09 (dt, 2H), 3.17–3.21 (dd, 1H), 3.35–3.43 (dd, 1H), 3.65 (m, 12H), 3.74–3.75 (dd, 1H), 3.80–3.82 (dd, 1H), 4.11–4.15 (dd, 2H), 5.19–4.25 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 23.4, 42.7, 45.6, 50.7, 63.7, 69.6, 70.4, 70.5 (m, 6C), 71.7, 156.4. HRMS (ESI) calcd for $C_{15}H_{29}O_6NNa$ $[M + Na]^+$ 342.1893, found 342.1894.

General procedure for the preparation of ω-(oxathilan-2-thione-5-yl)-α-oxazolidin-2-ones 3a–h from epoxyoxazolidinone 2a–d. The reaction was carried out under a nitrogen atmosphere. The solution of epoxyoxazolidinone **2a–d** (1 mmol) in 10 mL of anhydrous CH_2Cl_2 was to added lithium bromide (0.1 mmol, 0.086 g). After stirring the mixture at reflux for 0.5 h, a solution of carbon disulfide (1.1 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was then refluxed over 3–10 h (see Table 3). The reaction extent was monitored with TLC (Acetone / Ether: 60/40). At the end of the reaction, the mixture was cooled, diluted with water (40 mL), and then extracted with dichloromethane (4 × 40 mL). It was washed with water (2 × 30 mL) and dried on $MgSO_4$. The solvent was removed, and the residue was purified on column chromatography (eluent: acetone /ether: 60/40) to

obtain the ω-(oxathilan-2-thione-5-yl)-α-oxazolidin-2-ones **3a–h** as viscous oils.

General procedure one-pot three-component preparation of ω-(oxathilan-2-thione-5-yl)-α-oxazolidin-2-ones 3a–h. The reaction was carried out under a nitrogen atmosphere. The solution of oligoethylene glycols diglycidyl ether **1a–d** (3 mmol) in 10 mL of anhydrous THF was added to lithium bromide (0.3 mmol, 0.026 g). After stirring the mixture at reflux for 0.5 h, a solution of isocyanate (3.3 mmol) in dry THF (5 mL) was added dropwise. After the consummation of totally amount of isocyanate monitored by TLC (Acetone/Ether: 80/20), the mixture was cooled at room temperature, and 3.3 mmol of carbon disulfide was also added, and then, the reaction was left to stand at room temperature. After completion of the reaction, as indicated by TLC (Acetone/Ether: 60/40), the mixture was diluted with water (40 mL), and then extracted with dichloromethane (4 × 40 mL). It was washed with water (2 × 30 mL) and dried on $MgSO_4$. The solvent was removed, and the residue was purified on column chromatography (eluent: Acetone /Ether: 60/40) to obtain the ω-(oxathilan-2-thione-5-yl)-α-oxazolidin-2-ones **3a–h** as viscous oils.

5-(6-oxathiolan-2-thione-2,5-dioxahexan-5-yl)-3-phenyloxazolidin-2-one (3a). Colorless viscous oil, 235 mg, 60% yield. IR ($CHCl_3$) 1758 (C = O), 1420–1607 (C = C), 1140 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.37–3.58 (m, 2H), 3.61–3.70 (m, 4H), 3.72–3.80 (m, 2H), 3.89–3.94(m, 2H), 4.03–4.09 (m, 2H), 4.72–4.80 (m, 1H), 5.05–5.19 (m, 1H), 7.09–7.14 (m, 1H, Harom), 7.33–7.38 (m, 2H, Harom), 7.52–7.55 (m, 2H, Harom). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9, 46.8, 69.7, 69.9, 70.61 (m, 2C), 71.4, 89.5, 118.1 (s, 2C), 123.9, 129.0 (s, 2C), 138.1, 154.6, 212.2. HRMS (ESI) calcd for $C_{16}H_{19}O_5S_2NNa$ $[M + Na]^+$ 392.0602, found: 392.0605.

5-(9-oxathiolan-2-thione-2,5,8-trioxano nan-5-yl)-3-phenyl oxazolidin-2-one (3b). Colorless viscous oil, 296 mg, 68% yield. IR ($CHCl_3$) 1738 (C = O), 1452, 1609 (C = C), 1132 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.32–3.53 (m, 2H), 3.63–3.70 (m, 8H), 3.73–3.84 (m, 2H), 3.91–4.07(m, 2H), 4.10–4.23(m, 2H), 4.65–4.73 (m, 1H), 5.08–5.22 (m, 1H), 6.96–7.05 (m, 1H), 7.18–7.32 (m, 2H), 7.45–7.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9, 47.0, 69.4, 69.8, 70.6 (m, 4C), 71.3, 89.5, 118.3 (s, 2C), 124.1, 129.0 (s, 2C), 138.1, 154.8, 212.2. HRMS (ESI) calc for $C_{18}H_{23}O_6NS_2Na$ $[M + Na]^+$ 436.0864, found: 436.0866.

5-(12-oxathiolan-2-thione-2,5,8,11-tetra oxadodecan-5-yl)-3-phenyloxazolidin-2-one (3c). Colorless viscous oil, 364 mg, 76% yield. IR ($CHCl_3$) 1757 (C = O), 1453, 1609 (C = C), 1117 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.42–3.53 (m, 2H), 3.60–3.64(m, 8H), 3.68–3.75 (m, 2H), 3.81–3.87(m, 2H), 3.92–4.03(m, 2H), 4.68–4.75 (m, 1H), 5,13–5,24 (m, 1H), 7.01–7.09 (m, 1H, Harom), 7.29–7.38 (m, 2H, Harom), 7.46–7.52 (m, 2H, Harom). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7, 46.7, 69.6, 70.2, 70.5 (m, 4C), 71.4, 89.6, 118.2 (s, 2C), 124.0, 128.8 (s, 2C), 138.2, 154.5, 212.4. HRMS (ESI) calc for $C_{20}H_{27}O_7NS_2Na$ $[M + Na]^+$ 480.1127, found: 480.1126.

5-(15-oxathiolan-2-thione-2,5,8,11,14-penta oxapentadecan-5-yl)-3-phenyloxazolidin-2-one (3d). Colorless viscous oil, 450 mg, 86% yield. IR ($CHCl_3$) 1737 (C = O) 1453–1609 (C = C), 1115 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.41–3.51 (m, 2H), 3.60–3.66 (m, 16H), 3.68–3.71 (m, 1H), 3.73–3.76 (m, 1H), 3.81–3.87 (m, 1H), 3.90–3.96(m, 1H), 4.02–4.06 (m, 1H), 4.08–4.13(m, 2H), 4.74–4.81 (m, 1H), 5.22–5.29 (m, 1H), 7.09–7.14 (m, 1H, Harom), 7.33–7.38 (m, 2H, Harom), 7.53–7.55 (m, 2H, Harom). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9, 46.9, 69.8, 70.6 (m, 8C, CH_2O), 71.08, 71.3, 89.4, 118.0 (s, 2C), 123.8 (s, 1C), 128.9 (s, 2C), 138.2, 154.6, 212.2. HRMS (ESI) calc for $C_{22}H_{31}O_8NS_2Na$ $[M + Na]^+$ 524.1389, found: 524.1386.

5-(6-oxathiolan-2-thione-2,5,8-trioxanonan-5-yl)-3-cyclohexyloxazolidin-2-one (3e). Colorless viscous oil, 282 mg, 64% yield. IR ($CHCl_3$) 1719 (C = O), 1121 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03–1.11 (m, 1H), 1.21–1.36(m, 5H), 1.50–1.68 (m, 5H), 3.34–3.40 (m, 1H), 3.50–3.56(m, 2H), 3.64–3.66 (m, 8H), 3.68–3.72 (m, 2H), 3.75–3.83 (m, 2H), 4.06–4.14 (m, 2H), 4.67–4.78 (m, 1H), 5.15–5.23 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.4 (s, 2C), 29.6 (s, 2C), 33.3, 36.0, 49.8, 63.5; 69.8 (m, 6C), 70.5, 71.2, 89.3, 155.5, 212.1. HRMS (ESI) calc for $C_{18}H_{29}NO_6S_2Na$ $[M + Na]^+$ 442.1334, found: 442.1337.

5-(12-oxathiolan-2-thione-2,5,8,11-tetraoxa dodecan-5-yl)-3-cyclohexyloxazolidin-2-one (3f). Colorless viscous oil, 345 mg, 71% yield. IR ($CHCl_3$) 1720 (C = O), 1120 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06–1.11(m, 1H), 1.25–1.42 (m, 5H), 1.64–1.79 (m, 5H), 3.36–3.39(m, 1H), 3.53–3.59(m, 2H), 3.64–3.65 (m, 12H), 3.66–3.70 (m, 2H), 3.72–3.76 (m, 2H), 3.81–3.93 (m, 2H), 4.59–4.67 (m, 1H), 5.25–5.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 30.0 (s, 2C), 30.3 (s, 2C), 36,0, 42,5, 52,3, 69.8, 70.5 (m, 6C), 71.1, 71,7, 89.4, 157.0, 212.2. HRMS (ESI) calc for $C_{20}H_{33}NO_7S_2Na$ $[M + Na]^+$ 486,1596, found: 486.1593.

5-(6-oxathiolan-2-thione-2,5,8-trioxanonan-5-yl)-3-propyloxazolidin-2-one (3g). Colorless viscous oil, 229 mg, 57% yield. IR ($CHCl_3$) 1748 (C = O), 1116 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82–0.87 (t, 3H), 1.41–1.49(m, 2H), 3.04–3.09 (t, 2H), 3.52–3.61(m, 2H), 3.63–3.64 (m, 8H), 3.65–3.68 (m, 2H), 3.78–3.82 (m, 2H), 4.14–4.17 (m, 2H), 4.76–4.80 (m, 1H), 5.15–5.23 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 23.1, 36.1, 42.8, 63.7, 69.7; 69.8, 70.6 (m, 4C), 71.3, 89.2, 156.4, 212.0. HRMS (ESI) calc for $C_{15}H_{25}NO_6S_2Na$ $[M + Na]^+$ 402.1021, found: 402,1023.

5-(12-oxathiolan-2-thion-2,5,8,11-tetraoxa dodecan-5-yl)-3-propyloxazolidin-2-one (3h). Colorless viscous oil, 276 mg, 62% yield. IR ($CHCl_3$) 1723 (C = O), 1115 (C = S), cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90–0.95 (t, 3H), 1.52–1.64 (m, 2H), 3.19–3.24 (t, 2H), 3.58–3.63(m, 2H), 3.64–3.66 (m, 12H), 3.67–3.69 (m, 2H), 3.71–3.74 (m, 2H), 3.83–3.94 (m, 2H), 4.63–4.67 (m, 1H), 5.28–5.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 22.17, 35.89, 42.11, 62.8, 69.7, 69.8; 70.5 (m, 6C), 71.6, 89.6, 157.8, 212.4. HRMS (ESI) calc for $C_{17}H_{29}NO_7S_2Na$ $[M + Na]^+$ 446.5344, found: 446.5346.

Acknowledgments. The authors are grateful to the Tunisian Ministry of Higher Education and Scientific Research for financial support (LR99ES14) of this research and to Dr. M. A. Sanhoury, MRSC of the Department of Chemistry, Faculty of Sciences of Tunis for helpful discussions and technical assistance.

REFERENCES AND NOTES

[1] (a) Zhu, J.; Bienayme, H., Eds. Domino Reactions in Organic Synthesis; Wiley-VCH: Weinheim, 2005; (b) Tietze, L. F.; Brasche, G.;

Gericke, K. Eds. Multicomponent Reactions; Wiley-VCH: Weinheim, 2006; (c) Domling, U.; Ugi, I. Angew Chem, Int Ed 2000, 39, 3168; (d) Soleimani, E.; Khodaei, M. M.; Batooie, N.; Baghbanzadeh, M. Green Chem 2011, 13, 566.

[2] (a) Mudumala, V. R.; Chinthaparthi, R. R.; Yeon, T. J. Tetrahedron 2014, 70, 3762; (b) Qian, W.-Y.; Amegadzie, A.; Winternheimer, D.; Allen, J. Org Lett 2013, 15, 2986; (c) Luan, Y.; Yu, J.; Zhang, X.-W.; Schaus, S. E.; Wang, G. J Org Chem 2014, 79, 4694; (d) Arenas, D. R. M.; Kouznetsov, V. V. J. Org Chem 2014, 79, 5327.

[3] Park, C.; Brittelli, D.; Wang, C. L.; Marsh, F.; Gregory, W. A.; Wuonola, M. A. J Med Chem 1992, 35, 1156.

[4] Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R. J Med Chem 1996, 39, 673.

[5] D'Andrea, S.; Zheng, Z. B.; Den, B. K.; Fung-Tomc, J. C. Bio Org Med Chem Lett 2005, 15, 2834.

[6] Dresser, L. D.; Rybak, M. J. Pharmacothey 1998, 18, 456.

[7] Schindler, S. C.; Forster, M. P.; Carreira, M. C. Org Lett 2010, 12, 4102.

[8] (a) Katz, S. J.; Bergmeier, S. C. Tetrahedron Lett 2002, 43, 557; (b) Benedetti, F.; Norbedo, S. Tetrahedron Lett 2000, 41, 10071.

[9] (a) Gates, S. K.; Silverman, B. R. J Am Chem Soc 1989, 111, 8891; (b) Madar, J. D.; Kopecka, H.; Pireh, D.; Pease, J. Tetrahedron Lett 2001, 42, 3681.

[10] (a) Patel, U.; Yan, P. Y.; Hobbs, W. F.; Kaczmarczyk, J.; Slee, M. A. Biol Chem 2001, 276, 37199; (b) Seebach, D.; Beck, A. K.; Brenner, M.; Gaul, C.; Heckel, A. Chimia 2001, 55, 831.

[11] Ishii, T.; Nojiri, H.; Yamada, M.; Mizuguchi, R. Thermosetting resinous composition containing polyfunctional oxazolidinone terminated epoxy resins, June 28, 1994, US Patent 5324797.

[12] (a) Fugitt, R. B.; Martinelli, J. Pharma Sci 1973, 62, 1013; (b) Zurenko, G. E.; Yagi, B. H.; Schaadt, R. D.; Allison, J. W.; Kilburn, J. O.; Glickman, S. E. Antimicrob Agents Chemother 1996, 40, 839; (c) Lohray, B. B.; Lohray, V. B.; Sirvastava, B. K.; Gupta, S.; Solanki, M.; Kapadnis, P.; Takale, V.; Panday, P. Bioorg Med Chem Lett 2004, 14, 3139.

[13] Masocha, W.; Kombian, S. B.; Edafiogho, I. O. Eur J Med Chem 2009, 3, 967.

[14] Welstead, W. J. Jr.; Helsley, G. C.; Taylor, C. R.; Turnbull, L. B.; Da Vanzo, J. P.; Funderburk, W. H.; Alphin, R. S. J Med Chem 1973, 16, 1129.

[15] Harris, H. A.; Albert, L. M.; Leathurby, Y.; Malamas, M. S.; Mewshaw, R. E.; Miller, C. P.; Kharode, Y. P.; Marzolf, J.; Komm, B. S.; Winneker, R. C.; Frail, D. E.; Henderson, R. A.; Zhu, Y.; Keith, J. C. Endocrinology 2003, 144, 4241.

[16] Vera-Cabrera, L.; Gonzalez, E.; Rendon, A.; Ocampo-Candiani, J.; Welsh, O.; Victor, M. V.-M.; Choi, S. H.; Molina-Torres, C. Antimicrob Agents Chemother 2006, 50, 3170; (b) Fortún, J.; Martín-Dávila, P.; Navas, E.; Pérez-Elías, M.-J.; Cobo, J.; Tato, M.; De la Pedrosa, E. G.-G.; Gómez-Mampaso, E.; Moreno, S. J Antimicrob Chemother 2005, 56, 180.

[17] Ali, A.; Reddy, G. S. K. K.; Cao, H.; Anjum, S. G.; Nalam, M. N. L.; Schiffer, C. A.; Rana, T. M. J Med Chem 2006, 49, 7342.

[18] Momose, Y.; Maekawa, T.; Yamano, T.; Kawada, M.; Odaka, H.; Ikeda, H.; Sohda, T. J Med Chem 2002, 45, 1518.

[19] (a) Coston, A.; Gouret, C.; Raynavd, G. Act Neru Super (Praha) 1977, 2, 331; (b) Kekeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M. Osada J Antibiot 1998, 51, 1126.

[20] (a) Ochiai, B.; Endo, T. Prog Polym Sci 2005, 30, 183; (b) Pandey, K. K. Coord Chem Rev 1995, 140, 37; (c) Nakano, K.; Tatsumi, G.; Nozaki, K. J Am Chem Soc 2007, 129, 15116.

[21] (a) Motokucho, S.; Itagaki, Y.; Sudo, A.; Endo, T. J. Polym Sci Part A 2005, 43, 3711; (b). Maggi, R.; Malmassari, C. Oro, C. Pela, R. Sartori, G. Soldi, L. Synthesis 2008, 53; (c) Yavari, I.; Ghazanfarpour-Darjani, M.; Hossaini, Z. Sabbaghan, M. Hosseini, N. Synlett 2008, 889; (d) Halimehjani, Z. A. Ebrahim, F. Aziz, N. Saidi R. M. J Hetero Chem 2009, 46, 347; (e) Wang, Y.-M.; Li, B.; Wang, H.; Zhang, Z.-C.; Lu, X.-B. Appl Organomet Chem 2012, 26, 614.

[22] Marianucci, E.; Berti, C.; Pilati, F.; Manaresi, P. Polymer 1994, 35, 1564.

[23] (a) Kanemura, Y. Sasagawa, K. Kobayashi, S. European Patent Application, EP 528590, Al (1993); (b) Yean, L. Bochu C., European Patent Application, EP 408459 Al (1990); (c) Allcock, H. R.; Rutt, J. S. Macromolecules 1991, 24, 2852.

[24] Speranza, G. P.; Peppel, W. J. J. Org Chem 1958, 23, 1922.

[25] Herweh, J. E.; Kauffman, W. J. Tetrahedron Lett 1971, 12, 809.

[26] Herweh, J. E.; Foglia, T. A.; Swern, D. J Org Chem 1968, 33, 4029.

[27] Shibata, I.; Baba, A.; Iwasaki, H.; Matsuda, H. J Org Chem 1986, 51, 2177.

[28] Fujiwara, M.; Baba, A.; Tomohisa, Y.; Matsuda, H. Chem Lett 1986, 15, 1963.

[29] Qian, C.-T.; Zhu, D.-M. A Synlett 1994, 129.

[30] Zhang, X.; Chen, W.; Zhao, C.; Li, C.; Wu, X.; Chen, Z. W. Synth Commun 2010, 40, 3654.

[31] Wang, P.; Qin, J.; Yuan, D.; Wang, Y.; Yao, Y. Chem Catchem 2015, 7, 1145.

[32] Kondoh, A.; Odaira, K. Terada, M. Angewandte Chemie, 2015, 54, 11240.

[33] Laserna, V.; Guo, W.; Kleij, W. A. Adv Synth & Cat 2015, 13, 357 2849.

[34] Baronsky, T.; Beattie, C.; Harrington, W. R.; Irfan, R.; North, M.; Osende, G. J.; Young, C. ACS Catal 2013, 3, 790.

[35] Beattie, C.; North, M. RSC Adv 2014, 4, 31345.

[36] Charles, S.Y.; Dong, V. M., Synlett, 2011, 974.

[37] Beattie, C.; North, M. Chem CatChem 2014, 6, 1252.

[38] Choi, W.; Sanda, F.; Endo, T. Hetercycles 2000, 52, 125.

[39] Taguchi, Y.; Yasumoto, M.; Shibuya, I.; Suhara, Y. Bull Chem Soc Jpn 1989, 62, 474.

[40] Taguchi, Y.; Yasumoto, K.; Shibuya, I.; Suhara, Y. Bull Chem Soc Jpn 1987, 60, 727.

[41] Kihara, N. Nakawaki, Y. Endo, T. J Org Chem 1995, 60, 473.

[42] Hayashi, S.; Furukawa, M.; Fugino, Y.; Nakao, T.; Nakato, K. Chem Pharm Bull 1971, 19, 1594.

[43] Motokucho, S.; Takeuchi, D.; Sanda, F.; Endo, T. Tetrahedron 2001, 57, 7149.

[44] Aroua, L.; Baklouti, A. Synth Commun 2007, 37, 1935.

[45] Aroua, L.; Baklouti, A. Phosphorus, Sulfur, and Silicon 2007, 182, 2419–1942.

[46] Gu, X.-P.; Ikeda, I.; Okahara, M. Synthesis 1985, 649.