Scientific Review
ISSN(e): 2412-2599, ISSN(p): 2413-8835
Vol. 5, Issue. 1, pp: 19-23, 2019
URL: https://arpgweb.com/journal/journal/10
DOI: https://doi.org/10.32861/sr.51.19.23

Academic Research Publishing Group

Original Research **Open Access**

Synthesis of Some Unsymmetrical Dioxime Esters Using the Acetylacetone as a Precursor

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Abstract

Three unsymmetrical dioxime esters (2E,4E)-(4-imino O-benzoyl-2-imino O-terphthaloyl)pentane, (2E,4E)-(4-imino O-benzoyl-2-imino O-tosyl)pentane and (2E,4E)-(4-imino O-terphthaloyl-2-imino O-tosyl)pentane were obtained employing esterification process between (2E,4E)-pentane-2,4-dione O4-benzoyl dioxime 2 and terephthaloyl chloride or tosyl chloride. The third unsymmetrical dioxime ester was synthesized through similar esterification reaction between 4-(2E,4E)-4-(hydroxyimino)pentan-2-ylideneaminooxycarbonyl)benzoyl chloride 8 and tosyl chloride. The yields of these esterification reactions has been found to vary from moderate to very good yields giving single geometric isomers in all cases. The synthesis of these three unsymmetrical dioxime esters required, firstly, the synthesis of (2E,4E)-pentane-2,4-dione O4-benzoyl dioxime and 4- [(2E,4E)-4-(hydroxyimino)pentan-2-ylidene]amino oxycarbonylbenzoyl chloride as two precursors.

Keywords: Geometric isomers; Synthesis; Unsymmetrical; Dioxime esters.

1. Introduction

Oximes have been classified as useful molecules for protecting and purifying carbonyl compounds in organic chemistry [1]. These molecules have also shown antimicrobial, antioxidant, antitumor, antidepressive, antiviral agents and anticonvulsant properties [2-7]. Oximes have been reported to be good precursors for the synthesis amines that are used as paints, fibers, medical tools and in the synthesis of some lactams [8-11]. Oxime esters could be obtained by the reaction of keto- or aldoximes with acid chlorides or acid anhydrides. The oxime esters could also be used in the synthesis of peptides and fragrances [12, 13]. Oxime esters have also been reported to have cleavage impact on DNA [14-16], herbicidal as well as antitumor activities [17, 18]. Oxime esters are important intermediates for the synthesis of biologically active heterocyclic molecules [19]. Herein, unsymmetrical dioxime esters (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane, (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane and (2*E*,4*E*)-(4-imino *O*-terphthaloyl-2-imino *O*-tosyl)pentane have been synthesized.

2. Results and Discussion

The (*2E,4E*)-pentane-2,4-dione O^4-benzoyl dioxime **2** was prepared first to be the precursor for the synthesis of (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane **4**. A synthetic rout was followed in which one mole of the hydroxylamine hydrochloride was reacted with one mole of the (*E*)-4-(benzoyloxyimino)pentan-2-one **1** under basic conditions at ambient temperature. The desired (*2E,4E*)-pentane-2,4-dione O^4-benzoyl dioxime **2** was obtained in moderate yield (46%) as yellow oil. This was converted to the desired (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane **4**. Thus, a one mole of the (*2E,4E*)-pentane-2,4-dione O^4-benzoyl dioxime **2** was reacted with one mole of a solution of terphthaloyl chloride under basic conditions. The desired (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane **4** was obtained in very good yield (80%) as brown oil **(Scheme 1)**. In a similar approach, the (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane **6** was synthesized by reacting one mole of the (*2E,4E*)-pentane-2,4-dione O^4-benzoyl dioxime **2** with one mole of a solution of the tosyl chloride under the same conditions. The desired (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane **6** was obtained in good yield (70%) as dark brown oil

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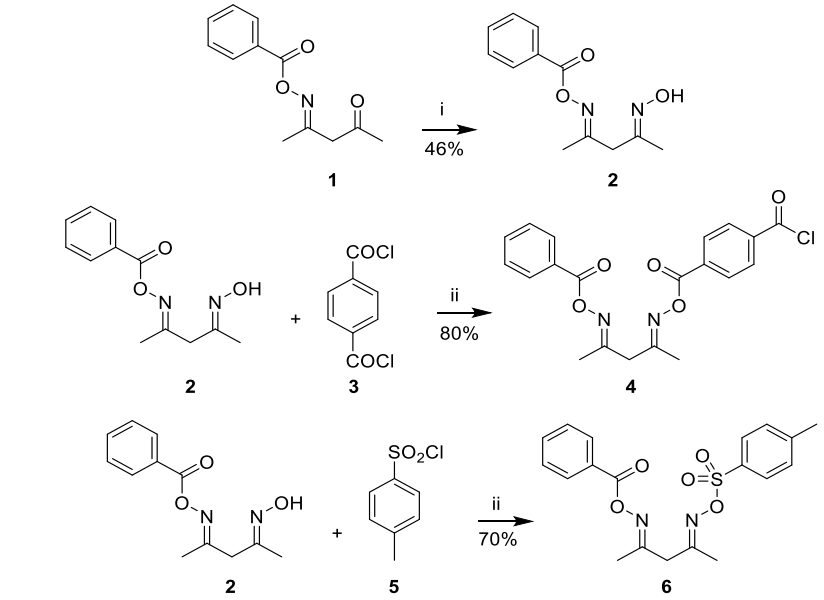
Scheme-1. The synthesis of (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane 4 and the (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane 6

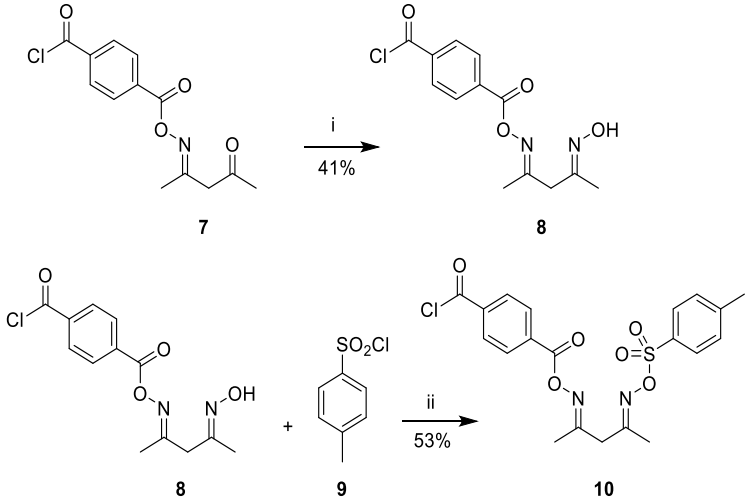


Reagents & reaction conditions: (i) $NH_2OH.HCl$, K_2CO_3, Na_2SO_4, rt, 45 min; (ii) Et_3N, $CHCl_3$, 0-7 °C, 30 min, then rt, 2 hrs

The analytical data that was collected from the IR, mass spectrometry and the ^{1}HNMR respectively revealed that the (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane **4** and the (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane **6** were formed. The ^{1}HNMR spectroscopic data confirmed the formation of single geometric isomer in both cases.

Likewise, the (2*E*,4*E*)-(4-imino *O*-terphthaloyl-2-imino *O*-tosyl)pentane **10** was synthesized throughout a similar approach. The mono oxime terphthaloyl mono ester **8** was prepared first to be the precursor for the synthesis of compound **10**. The synthesis of the precursor **8** was carried out by reacting one mole of hydroxylamine hydrochloride with (*E*)-4-(4-oxopentan-2-iminocarbonyl) benzoyl chloride **7** under basic conditions and the reactants were ground at room temperature for 30 min. The desired monoterphthaloyl oxime ester **10** was obtained in moderate yield (41%) as light yellow oil **(Scheme 2)**. The resulting monoterphthaloyl oxime ester **8** was immediately taken in the next step, as is, to synthesize the desired (2*E*,4*E*)-(4-imino *O*-terphthaloyl-2-imino *O*-tosyl)pentane **10**. One mole of the terphthaloyl mono ester **8** was reacted with a solution of one mole of *p*-toluene sulphonyl chloride in chloroform under mild basic conditions to obtain the desired oxime ester **10** in moderate yield (53%) as dark brown oil

Scheme-2. the synthesis of (2*E*,4*E*)-(4-imino *O*-terphthaloyl-2-imino *O*-tosyl)pentane 10



Reagents & reaction conditions: (i) $NH_2OH.HCl$, K_2CO_3, Na_2SO_4, rt, 30 min; (ii) Et_3N, $CHCl_3$, 0 - 7 °C, 30 min, then rt, 2 hrs

The spectroscopic data for the resulting (2*E*,4*E*)-(4-imino *O*-terphthaloyl-2-imino *O*-tosyl)pentane **10** revealed that the unsymmetrical dioxime ester **10** was successfully formed. The ^{1}HNMR data confirmed the formation of the (2*E*,4*E*)-(4-imino *O*-terphthaloyl-2-imino *O*-tosyl)pentane **10** as a single geometric isomer.

3. Experimental

3.1. Materials

Acetyl acetone, hydroxylamine hydrochloride, benzoyl chloride, terphthaloyl chloride, *p*-toluene sulphonyl chloride, potassium carbonate, anhydrous sodium sulphate, triethylamine and chloroform were purchased from P K Park and used without further purification.

3.2. Instrumentation

Melting points were measured on a Barnstead electrothermal IA 9100. ^{1}HNMR spectrum was recorded on a Bruker Avance 300 spectrometer. Residual proton signal from the deuteriated solvent was used as reference [DMSO (^{1}H, 2.50 ppm)]. Infrared spectrum was recorded on Jasco FT/IR-4100 Fourier transform infrared spectrometer. Mass spectrum was recorded on a Micromass Autospec M spectrometer.

3.3. Synthesis of (*E*)-4-(Hydroxyimino) Pentan-2-One

An literature procedure [20] was followed for the synthesis of the entitled compound. Hydroxylamine hydrochloride (6.94 g, 100 mmol), acetyl acetone (10 g, 100 mmol) and potassium carbonate (13.80 g, 100 mmol) in the presence of anhydrous sodium sulphate (14.20 g, 100 mmol) were placed in a mortar and ground at room temperature for 30 min. Chloroform (20 cm^3) was then added to the resulting paste, filtered and the solvent was evaporated *in vacuo*. The desired mono ketoxime was obtained, as two isomeric forms (*E*)-4-(hydroxyimino)pentan-one and (*Z*)-4-(hydroxyimino)pentan-one in ratio of (9:1), in low yield (3.10 g, 26.95 mmol, 27%) as yellow oil. The product was clean enough to be taken into the next synthetic step. IR ν_{max} (cm^{-1}) 3298 (OH), 2987 (C-H), 2922 (C-H), 1710 (C=O), 1601 (C=N). ^{1}HNMR (DMSO-d6, 400 MHz) **Major isomer (I, formation ratio of 89.2%):** δ 8.181 (1H, s, O*H*), 1.87 (3H, s, CH_3), 1.74 (2H, s, CH_2), 1.45 (3H, s, CH_3); **Minor isomer (II, formation ratio of 10.8%):** δ 5.98 (1H, s, O*H*), 2.81 (3H, s, CH_3), 2.63 (2H, s, CH_2), 2.69 (3H, s, CH_3). Mass spec m/z ($C_5H_9NO_2$, MWt 115.13) 115 (59%), 98 (72%), 82 (100%), 73 (79%), 59 (82%).

3.4. Synthesis of (*E*)-4-(Benzoyloxyimino) Pentan-2-one1

An literature procedure [20] was followed for the synthesis of the entitled compound. (*E*)-4-(hydroxyimino)pentan-2-one (3.45 g, 30.0 mmol) in chloroform (40 cm^3) in the presence of triethyl amine (4.04 g, 40.0 mmol) were placed in a round-bottomed flask and stirred at 0 – 7 °C. A solution of benzoyl chloride (4.49 g, 32.0 mmol) in chloroform (50 cm^3) was then added dropwise over 30 min. The reaction mixture was left stirring at room temperature for 2 hours, after which distilled water (30 cm^3) was added to the mixture and stirred for further 10 min. The organic layer was extracted, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* to obtain the desired oxime ester **1** in moderate yield (3.20 g, 14.61 mmol, 49%) as dark oil. The product did not require further purification. IR ν_{max} (cm^{-1}) 3065 (C-H), 2980 (C-H), 1784 (C=O), 1717 (C=O), 1598 (C=N). ^{1}HNMR (DMSO-d6, 400 MHz) **Major isomer (*Z*-isomer, formation percentage of 91.0%):** δ 8.25 (2H, s, CH_2), 7.99 – 7.96 (2H, m, 2 × Ar-*H*), 7.56 – 7.47 (3H, m, 3 × Ar-*H*), 2.21 (3H, s, CH_3), 2.09 (3H, s, CH_3); **Minor isomer (*E*-isomer, formation percentage of 9.0%):** δ 8.60 (2H, s, CH_2), 8.10 – 8.00 (2H, m, 2 × Ar-*H*), 7.70 – 7.50 (3H, m, 3 × Ar-*H*), 3.65 (3H, s, CH_3), 3.48 (3H, s, CH_3). Mass spec m/z ($C_{12}H_{13}NO_3$, MWt 219.24) 219 (52%), 202 (88%), 159 (65%), 122 (60%), 105 (100%).

3.5. Synthesis of (*E*)-4-(4-Oxopentan-2-Iminocarbonyl) Benzoyl Chloride 7

An literature procedure [20] was followed for the synthesis of the entitled compound. (*E*)-4-(hydroxyimino)pentan-2-one (3.45 g, 30.0 mmol) in chloroform (40 cm^3) in the presence of triethyl amine (4.04 g, 40.0 mmol) were placed in a round-bottomed flask and stirred at 0 – 7 °C. A solution of terphthaloyl chloride (6.52 g, 32.0 mmol) in chloroform (50 cm^3) was then added dropwise over 30 min. The reaction mixture was left stirring at room temperature for 2 hours, after which a distilled water (30 cm^3) was added to the mixture and stirred for further 10 min. The organic layer was extracted, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* to obtain the desired oxime ester **7** in moderate yield (3.0 g, 10.65 mmol, 36%) as thick pink oil. The product did not require further purification. IR ν_{max} (cm^{-1}) 2980 (C-H), 2936 (C-H), 1778 (COCl), 1720 (C=O, oxime ester), 1612 (C=O, remaining ketonic group), 1600 (C=N). ^{1}HNMR (DMSO-d6, 400 MHz) δ 8.27 (2H, s, CH_2), 8.04 – 8.02 (4H, m, 4 × Ar-*H*), 2.32 (3H, s, CH_3), 2.15 (3H, s, CH_3).

3.6. Synthesis of (2*E*,4*E*)-(4-imino *O*-Benzoyl-2-Imino *O*-Terphthaloyl) Pentane 4

An literature procedure [20] was followed for the synthesis of the entitled compound. The mono oxime benzoyl mono ester **2** was prepared first to be the precursor for the synthesis of compound **4**. Hydroxylamine hydrochloride (2.08 g, 30 mmol), mono oxime mono benzoyl ester **1** (6.57 g, 30 mmol) and potassium carbonate (4.14 g, 30 mmol) in the presence of anhydrous sodium sulphate (4.26 g, 30 mmol) were placed in a mortar and ground at room temperature for 30 min. Chloroform (20 cm^3) was then added to the resulting paste, filtered and the solvent was evaporated *in vacuo*. The desired dioxime mono benzoyl ester **2** was obtained in moderate yield (3.20 g, 13.67 mmol, 46%) as yellow oil. This was taken in the next step, as is, to synthesize the desired (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane **4**. Thus, the dioxime mono benzoyl ester **2** (3.0 g, 12.82 mmol) was dissolved in chloroform (40 cm^3) in the presence of triethyl amine (1.29 g, 12.82 mmol) were placed in a round-bottomed flask and stirred at 0 – 7 °C. A solution of terphthaloyl chloride (2.60 g, 12.82 mmol) in chloroform (50

cm^3) was then added dropwise over 30 min. The reaction mixture was left stirring at room temperature for 2 hours, after which distilled water (30 cm^3) was added to the mixture and stirred for further 10 min. The organic layer was extracted, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* to obtain the desired oxime esters **4** in a very good yield (4.10 g, 10.23 mmol, 80%) as brown oil. The product did not require further purification. IR ν_{max} (cm^{-1}) 2980 (C-H), 2933 (C-H), 1788 (C=O), 1778 (C=O), 1717 (C=O), 1605 (C=N), 1574 (C=N). ^{1}HNMR (DMSO-d6, 400 MHz) δ 8.28 (2H, s, C*H*$_2$), 7.94 (1H, d, 1 × Ar-*H*), 7.55 – 7.48 (6H, m, 6 × Ar-*H*), 7.15 (2H, d, 2 × Ar-*H*), 2.28 (6H, 2 × C*H*$_3$). Mass spec m/z ($C_{20}H_{17}ClN_2O_5$, MWt 400.82) 403 (52%), 401 (60%), 262 (89%), 172 (59%), 91 (100%).

3.7. Synthesis of (2*E*,4*E*)-(4-Imino *O*-Benzoyl-2-Imino *O*-Tosyl) Pentane 6

An literature procedure [20] was followed for the synthesis of the entitled compound. The mono oxime benzoyl mono ester **2** was prepared first to be the precursor for the synthesis of compound **4**. Hydroxylamine hydrochloride (2.08 g, 30 mmol), mono oxime mono benzoyl ester (6.57 g, 30 mmol) and potassium carbonate (4.14 g, 30 mmol) in the presence of anhydrous sodium sulphate (4.26 g, 30 mmol) were placed in a mortar and ground at room temperature for 30 min. Chloroform (20 cm^3) was then added to the resulting paste, filtered and the solvent was evaporated *in vacuo*. The desired dioxime mono benzoyl ester **2** was obtained in moderate yield (3.20 g, 13.67 mmol, 46%) as yellow oil. This was taken in the next step, as is, to synthesize the desired (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane **6**. Thus, the dioxime mono benzoyl ester **2** (3.0 g, 12.82 mmol) wa dissolved in chloroform (40cm^3) in the presence of triethyl amine (1.29 g, 12.82 mmol) were placed in a round-bottomed flask and stirred at 0 – 7 °C. A solution of *p*-toluene sulfonyl chloride (2.44 g, 12.82 mmol) in chloroform (50 cm^3) was then added dropwise over 30 min. The reaction mixture was left stirring at room temperature for 2 hours, after which distilled water (30 cm^3) was added to the mixture and stirred for further 10 min. The organic layer was extracted, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* to obtain the desired oxime esters **6** in a good yield (3.50 g, 9.02 mmol, 70%) as dark brown oil. The product did not require further purification. IR ν_{max} (cm^{-1}) 2980 (C-H), 2926 (C-H), 1747 (C=O), 1717 (C=N), 1615 (C=N), 1371 (O=S=O). ^{1}HNMR (DMSO-d6, 400 MHz) δ 8.22 (2H, s, C*H*$_2$), 7.93 (1H, d, 1 × Ar-*H*), 7.53 – 7.47 (6H, m, 6 × Ar-*H*), 7.13 (2H, d, 2 × Ar-*H*), 2.27 (6H, s, 2 × C*H*$_3$). Mass spec m/z ($C_{19}H_{20}N_2O_5S$, MWt 388.44) 388 (51%), 320 (70%), 122 (62%), 109 (100%).

3.8. Synthesis of (2*E*,4*E*)-(4-Imino *O*-Terphthaloyl-2-Imino *O*-Tosyl)Pentane 10

An literature procedure [20] was followed for the synthesis of the entitled compound. The mono oxime terphthaloyl mono ester **8** was prepared first to be the precursor for the synthesis of compound **10**. Hydroxylamine hydrochloride (1.48 g, 21.30 mmol), (*E*)-4-(4-oxopentan-2-iminocarbonyl) benzoyl chloride **7** (5.99 g, 21.30 mmol) and potassium carbonate (2.93 g, 21.30 mmol) in the presence of anhydrous sodium sulphate (3.02 g, 21.30 mmol) were placed in a mortar and ground at room temperature for 30 min. Chloroform (20 cm^3) was then added to the resulting paste, filtered and the solvent was evaporated *in vacuo*. The desired dioxime mono terphthaloyl ester **8** was obtained in moderate yield (2.60 g, 8.76 mmol, 41%) as light yellow oil. This was taken in the next step, as is, to synthesize the desired (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane **10**. Thus, the mono oxime terphthaloyl mono ester **8** (2.49 g, 8.40 mmol) was dissolved in chloroform (40 cm^3) in the presence of triethyl amine (0.84 g, 8.40 mmol) were placed in a round-bottomed flask and stirred at 0 – 7 °C. A solution of *p*-toluene sulfonyl chloride (1.60 g, 8.40 mmol) in chloroform (50 cm^3) was then added dropwise over 30 min. The reaction mixture was left stirring at room temperature for 2 hours, after which distilled water (30 cm^3) was added to the mixture and stirred for further 10 min. The organic layer was extracted, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* to obtain the desired oxime ester **10** in moderate yield (2.0 g, 4.43 mmol, 53%) as dark brown oil. The product could be purified by column chromatography using an eluent of ethyl acetate and petroleum ether in ratio of (3:1 v/v). IR ν_{max} (cm^{-1}) 2980 (C-H), 2933 (C-H), 1717 (C=O), 1612 (C=N), 1610 (C=N), 1368 (O=S=O). ^{1}HNMR (DMSO-d6, 400 MHz) δ 8.27 (2H, s, C*H*$_2$), 8.04 (1H, d, 1 × Ar-*H*), 7.53 (4H, d, 4 × Ar-*H*), 7.14 (4H, d, 4 × Ar-*H*), 2.30 (3H, s, C*H*$_3$), 2.28 (3H, s, C*H*$_3$), 2.12 (3H, s, C*H*$_3$). Mass spec m/z ($C_{20}H_{19}ClN_2O_6S$, MWt 450.89) 450 (51%), 452 (53%), 319 (74%), 295 (58%), 91 (100%).

4. Conclusion

The three aimed unsymmetrical dioxime esters (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-terphthaloyl)pentane, (2*E*,4*E*)-(4-imino *O*-benzoyl-2-imino *O*-tosyl)pentane and (2*E*,4*E*)-(4-imino *O*-terphthaloyl-2-imino *O*-tosyl)pentane were synthesized employing straightforward esterification process between (*2E*,*4E*)-pentane-2,4-dione O^4-benzoyl dioxime **2** and terephthaloyl chloride or tosyl chloride for the first two unsymmetrical dioxime etsers. The third unsymmetrical dioxime ester was synthesized by reacting 4-(2*E*,4*E*)-4-(hydroxyimino)pentan-2-ylideneaminooxycarbonyl)benzoyl chloride **8** with tosyl chloride. Single geometric isomers of the desired unsymmeterical dioxime esters were obtained in moderate to very good yields.

Acknowledgments

Authors would like to thank the Department of Chemistry, Faculty of Science, Misurata University for supporting this work.

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