Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

Selenium dioxide reaction of substituted diphenacyl sulfides: generation of α -ketoacids

Muthupandi Nagaraj[a], Devanathan Perumal[a], Muthusamy Boominathan[a], Shanmugam Muthusubramanian[a] & Nattamai Bhuvanesh[b]

[a] Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India

[b] X-Ray Diffraction Lab, Department of Chemistry, Texas A&M University, College Station, TX 77842, USA

Published online: 15 Mar 2013.

To cite this article: Muthupandi Nagaraj, Devanathan Perumal, Muthusamy Boominathan, Shanmugam Muthusubramanian & Nattamai Bhuvanesh (2014) Selenium dioxide reaction of substituted diphenacyl sulfides: generation of α -ketoacids, Journal of Sulfur Chemistry, 35:1, 24-30, DOI: 10.1080/17415993.2013.769542

To link to this article: http://dx.doi.org/10.1080/17415993.2013.769542

Journal of Sulfur Chemistry, 2014
Vol. 35, No. 1, 24–30, http://dx.doi.org/10.1080/17415993.2013.769542

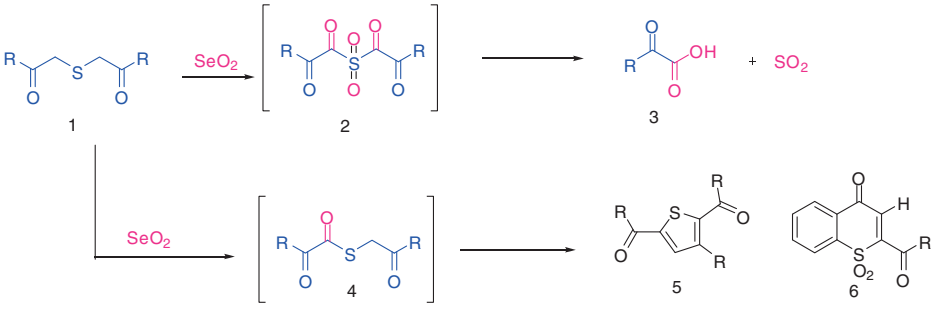
Selenium dioxide reaction of substituted diphenacyl sulfides: generation of α-ketoacids

Muthupandi Nagaraj[a], Devanathan Perumal[a], Muthusamy Boominathan[a], Shanmugam Muthusubramanian[a]* and Nattamai Bhuvanesh[b]

[a]*Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India;* [b]*X-Ray Diffraction Lab, Department of Chemistry, Texas A&M University, College Station, TX 77842, USA*

(*Received 19 November 2012; final version received 20 January 2013*)

The attempted selenium dioxide oxidation of substituted diphenacyl sulfides in anticipation of further functionalization led to a series of α-ketoacids **3** via oxidation followed by C−S bond cleavage. Two minor products, **5** and **6**, have also been isolated and a mechanistic pathway for the formation of **3**, **5** and **6** has been proposed.



Keywords: diphenacyl sulfides; α-ketoacids; oxidation; 2-oxo-2-arylacetic thioanhydride; selenium dioxide

1. Introduction

Selenium dioxide, which is used as a key component in the chemistry reported in this manuscript, is a very useful and versatile reagent for the synthesis of various types of organic compounds. The reagent is particularly useful for allylic oxidation (*1*) and oxidation of reactive methylenes (*2*). However, when coupled with other reagents such as acetic acid (*3*), acetic anhydride (*4*) or chlorotrimethylsilane (*5*), it is also employed for other useful transformations. Triselenium dicyanide is formed by the reaction of malononitrile and selenium dioxide, which is used as a selenocyanating reagent (*6*). In addition, selenium-containing heterocyclic compounds are of

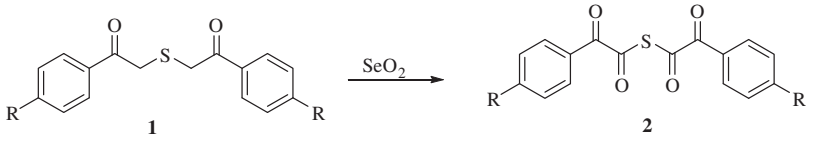
*Corresponding author. Email: muthumanian2001@yahoo.com

interest due to their biological and synthetic applications. In particular, 1,2,3-selenadiazole and its derivatives are well known and have attracted attention as versatile synthetic intermediates (*7*). Recently, a series of α-ketoamides were synthesized via selenium dioxide-mediated oxidative amidation between arylglyoxals and secondary amines, which was accelerated by microwave irradiation (*8*).

α-Ketoacids, the products of the new reactions described in this manuscript, are versatile compounds used as intermediates for the synthesis of variety of substances. They are of great interest in medicinal chemistry, and this structural scaffold represents a key framework of many biologically active agents in natural products (*9*). α-Ketoacids are used primarily as energy for liver cells and in fatty acid synthesis. Oxoacid participates in an atom-economical alternative cycle by which plants and bacteria convert fatty acids into carbohydrates (*10*).

2. Results and discussion

We are interested in the reaction of selenium dioxide with compounds having active methylene group to generate new heterocycles (*11*). Previously, it has been shown that α-bromoketones undergo selenium dioxide oxidation to yield reactive 2-oxo-2-arylacetyl bromides, which are trapped by aryl-1,2-diamines, 1,2-aminophenol or 1,2-aminothiophenol to give quinoxalinones, benzoxazinones and benzothiazinones in good yields (*12*). In this connection, it was planned to investigate the reaction of diphenacyl sulfide with selenium dioxide. The intention was to prepare 2-oxo-2-arylacetic thioanhydride **2** as potential precursors for different heterocycles (Scheme 1). To our surprise, however, instead of the anticipated 1,2,4,5-tetraketone **2**, α-ketoacids **3** were obtained as the major products via oxidation followed by C−S bond cleavage.



1

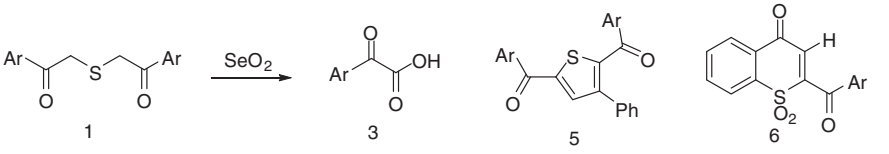
2

1a R= H
1b R=Cl,
1c R=Br,
1d R=OMe,
1e R=Ph

Scheme 1. Anticipated product.

To begin our studies, diphenacyl sulfide **1a** (0.5 mmol), selenium dioxide (1.5 mmol) and dioxane (10.0 mL) were taken together in a 50.0 mL RB flask and refluxed for 2 h. The course of the reaction was monitored by TLC. After 2 h, all of the reactants vanished and three new spots were detected by TLC. Compound **3** was subsequently isolated in good yield, while two other compounds, **5** and **6**, were detected in trace amounts but could only be isolated in a few cases. In the case of **1b**, only compound **5** could be isolated. In the case of **1a**, compounds **5** and **6** were both isolated. However, in all the cases (**1a**–**1e**), compound **3** was isolated in very good yield (more than 80%, Scheme 2).

Compounds **3**, **5** and **6** were characterized by their nuclear magnetic resonance (NMR) spectra. The ^{1}H NMR spectrum of **3b** in $CDCl_3$ has two 2H doublets at 7.48 and 8.20 ppm. The absence of peaks in the aliphatic region indicates that both the methylene groups of the sulfide **1b** are missing and presumably oxidized. A signal in the downfield region (nearly at 7 ppm), which gets exchanged with D_2O, was also noticed in all the cases. In the ^{13}C NMR spectrum of **3b**, only six



Scheme 2. Reaction of substituted diphenacyl sulfides with selenium dioxide.

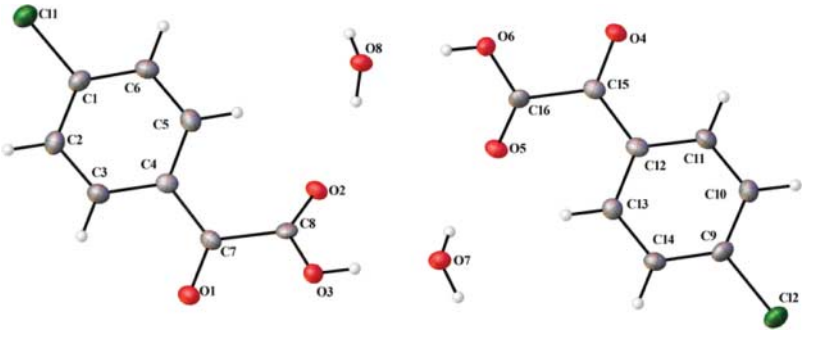


Figure 1. ORTEP diagram of **3b**.

signals were observed, two of them are assignable to carbonyl carbon signals appearing at 183.7 and 162.1 ppm. In the DEPT-135 spectrum, two CH carbons and four quaternary carbons could be located. The mass spectrum of compound **3b** appears to have a molecular ion peak at m/e 183.0 (M^-). The presence of two carbonyl groups, one aryl ring and replaceable hydrogen indicate that the compound obtained could be an *alpha* keto acid. Unambiguous evidence for the formation of an arylglyoxalic acid was obtained by single crystal X-ray analysis of **3b** (Figure 1).[1] This acid exists in a dimeric hydrated form as revealed by the solid state structural analysis.

The structure of **5** has been confirmed by the spectral data (*13*). The ^{1}H NMR spectrum of **6a** in $CDCl_3$ has a 1H singlet at 8.57 ppm, a 2H doublet at 8.14 ppm, a 1H doublet at 7.92 ppm, a 1H triplet at 7.64 ppm, a 3H multiplet between 7.54 and 7.59 ppm, and a triplet of doublet at 7.32 ppm. The presence of one benzoyl group and one benzo group are clearly evident from this data. The ^{13}C NMR spectrum of **6a** has 14 signals. The two carbonyl carbon signals appear at 189.3 and 192.1 ppm. In the DEPT-135 spectrum, eight CH carbons and six quaternary carbons were observed and the HMBC spectrum of **6a** has contours connecting the deshielded singlet at 8.57 ppm with the carbon at 189.3 ppm revealing that this hydrogen is in β-position to the benzoyl group. The doublet at 8.14 ppm gives HMBC contour with the carbons at 189.3, 133.7 and 127.3 ppm. These connectivities clearly suggest the possible structures for **6** shown in Figure 2. The infrared (IR) spectrum of **6a** shows absorptions at 1132 and 1328 cm^{-1} due to symmetric and asymmetric stretching vibrations of sulfone moiety. The mass spectrum of compound **6a** has the molecular ion peak at 316.25 ($M^- + H_2O$ adduct), proving that the product is a sulfone and not a sulfide or sulfoxide.

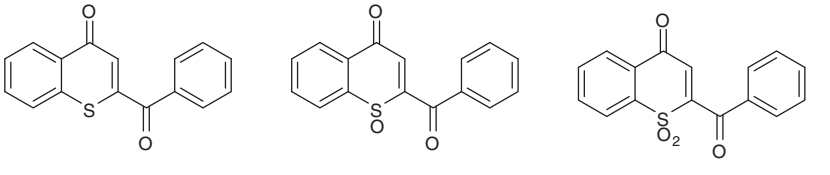
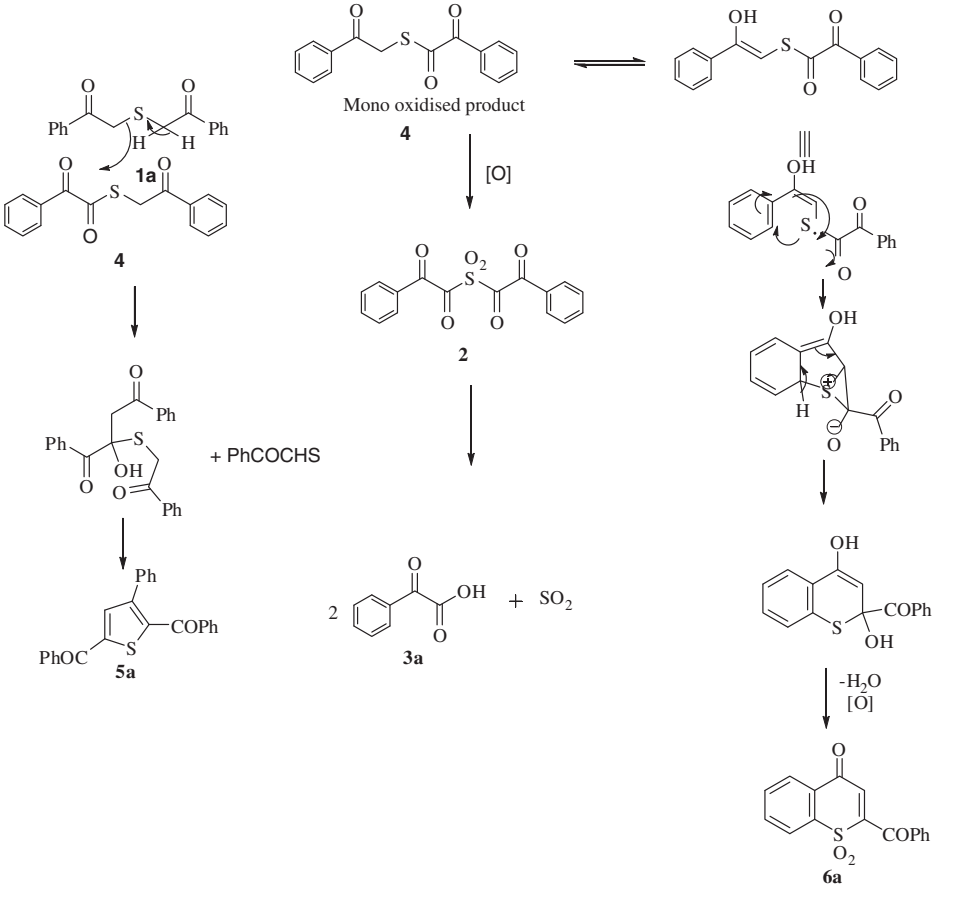


Figure 2. Possible structures for **6a**.

Thus, oxidations of substituted diphenacyl sulfides by selenium dioxide produced three products **3**, **5** and **6**. Unfortunately, none of these is the expected polyketone targeted during this investigation. Nevertheless, the oxidation to give the major product **3** is an interesting process and a potentially important pathway to these compounds. The formation of **3** is best visualized as occurring by initial oxidation of **1** to 1,2,4,5-tetraketone **2** followed by the selenium dioxide-induced C−S bond cleavage. The smell of sulfur dioxide noticed during the reaction also lends support to an oxidative cleavage of the C−S bond during the reaction.

The minor product**5** observed in two cases has previously been obtained from **1** by a self-condensation process catalysed by a base (*13*). In our laboratory, we have also noticed that prolonged exposure of **1** to atmospheric oxygen also led to slow formation of **5**. We suggest that selenium dioxide oxidation of **1** at one methylene group generates diketone **4** that serves as a precursor for **5** as shown in Scheme 3. The elimination of PhCOCHS noticed in this case has been already observed in some other reactions carried out in our laboratory (*14*).



Scheme 3. Proposed mechanism for the formation of **3**, **5** and **6**.

The formation of **6a** from **1a**, though in a minor amount, is an interesting feature of the investigation. We speculate that the formation of **6** can be explained by the mechanism shown in Scheme 3. The key intermediate in this mechanism is the diketone **4**. The tautomeric form of **4** could undergo an unusual intramolecular rearrangement involving a nucleophilic addition to the

aromatic ring by the sulfur and formation of a transient positively charged thiirane intermediate. This rearrangement is presumably aided by the conjugation present and the electrophilicity of the carbonyl. The final product could then be formed by rearomatization, cleavage of the thiirane, dehydration and finally oxidation to the sulfone.

3. Conclusion

In conclusion, we have investigated the selenium dioxide mediated oxidation of substituted diphenacyl sulfides. The investigation has led to a simple method for the synthesis of α-ketoacids.

4. Experimental

4.1. *General information*

NMR (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker 300 MHz NMR spectrometer in $CDCl_3$ using TMS as internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (J values) are reported in Hertz (Hz). ^{13}C NMR spectra were routinely run with broadband decoupling. IR spectra were recorded on a Shimadzu FT-IR instrument (in KBr pellets). Melting points were determined on a melting point apparatus equipped with a thermometer and were uncorrected. Column chromatography was carried out in silica gel (60–120 mesh) using pet ether–ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 series II Elemental CHNS analyzer. Mass analyses were performed on a liquid chromatography-ion trap mass spectrometer (LCQ Fleet, Thermo Fisher Instruments Limited, USA). The samples were introduced into the ion source by infusion method at flow rate 1 μL/min. The capillary voltage of the mass spectrometer was 33 V, with source voltage 4.98 kV for the mass scale (m/z 100–500 and 50–500).

4.2. *General procedure for selenium dioxide oxidation of diphenyl sulfide*

Selenium dioxide (1.5 mmol) was dissolved in dioxane (10.0 mL) and added to a 50 mL RB flask. To this, diphenacyl sulfide derivative **1** (0.5 mmol) was added and the mixture refluxed for 2 h. The course of the reaction was monitored by TLC. After completion, the reaction mixture was filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography using petroleum ether and ethyl acetate mixture (90:10) as the eluent to get **3**/**5**/**6**.

4.2.1. *2-Oxo-2-phenylacetic acid (15)* ***(3a)***

Colorless solid; isolated yield 71%; mp 64–66°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.50$ (2H, t, $J = 7.2$ Hz, CH), 7.64–7.66 (1H, m, CH), 8.16 (2H, d, $J = 7.2$ Hz, CH), 9.45 (1H, bs, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 128.8$ (2CH), 130.5 (2CH), 131.9 (C), 135.2 (C), 163.7 (C=O), 185.6 (C=O).

4.2.2. *2-(4-Chlorophenyl)-2-oxoacetic acid* ***(3b)***

Colorless solid; isolated yield 78%; mp 72–74°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$ (1H, bs, COOH), 7.50 (2H, d, $J = 8.4$ Hz, CH), 8.20 (2H, d, $J = 8.4$ Hz, CH); ^{13}C NMR (75 MHz,

$CDCl_3$): $\delta = 129.4$ (2CH), 130.2 (2CH), 132.4 (C), 142.5 (C), 162.1 (C=O), 183.7(C=O); Mass m/e 183 (M).

4.2.3. *2-(4-Bromophenyl)-2-oxoacetic acid* ***(3c)***

Colorless solid; isolated yield 82%; mp 76–78°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.31$ (1H, bs, COOH), 7.67 (2H, d, $J = 8.4$ Hz, CH), 8.12 (2H, d, $J = 8.4$ Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 129.4$ (2CH), 130.2 (2CH), 132.4 (C), 142.5 (C), 162.1 (C=O), 183.7 (C=O).

4.2.4. *2-(4-Methoxyphenyl)-2-oxoacetic acid* ***(3d)***

Colorless solid; isolated yield 72%; mp 58–60°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.89$ (3H, s, OCH_3), 6.96 (2H, d, $J = 9.0$ Hz, CH), 8.24 (2H, d, $J = 9.0$ Hz, CH) 9.85 (1H, bs, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.6$ (OCH_3), 114.3 (2CH), 124.7 (2CH), 133.7 (C), 163.9 (C), 165.5 (C=O), 183.2 (C=O).

4.2.5. *2-(Biphenyl-4-yl)-2-oxoacetic acid* ***(3e)***

Colorless solid; isolated yield 76%; mp 78–80°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.06$ (1H, bs, COOH), 7.43–7.51 (3H, m, CH), 7.64 (2H, d, $J = 7.5$ Hz, CH), 7.74 (2H, d, $J = 8.1$ Hz, CH), 8.39 (2H, d, $J = 8.1$ Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 127.4$ (2CH), 127.5 (2CH), 128.5 (CH), 128.8 (2CH), 130.5 (2CH), 131.9 (C), 139.4 (C), 148.3 (C), 161.6 (C=O), 189.8 (C=O); Anal. Calcd for $C_{14}H_{10}O_3$ (226.23): C, 74.33; H, 4.46%; found: C, 74.11; H, 4.38%.

4.2.6. *(3-Phenylthiophene-2,5-diyl)bis(phenylmethanone)* ***(5a)***

Colorless solid; isolated yield 10%; mp 152–154°C (156°C lit) (*13*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.17$–7.18 (2H, m, CH), 7.24–7.27 (4H, m, CH), 7.35–7.43 (2H, m, CH), 7.50–7.62 (3H, m, CH), 7.70 (2H, d, $J = 8.1$ Hz, CH), 7.75 (1H, s, CH), 7.95 (2H, d, $J = 8.1$ Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 127.9$, 128.0, 128.2, 128.5, 128.8, 129.6, 132.6, 132.9, 134.6, 135.6, 135.7, 136.7, 137.4, 142.6, 144.7, 145.6, 187.6 (C=O), 189.8 (C=O); Anal. Calcd for $C_{24}H_{16}O_2S$ (368.45): C, 78.24; H, 4.38; S, 8.70%; found: C, 78.02; H, 4.31; S, 8.61%.

4.2.7. *(3-(4-Chlorophenyl)thiophene-2,5-diyl)bis((4-chlorophenyl) methanone)* ***(5b)***

Colorless solid; isolated yield 11%; mp 170–172°C (174°C lit) (*13*); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$–7.23 (4H ,m, CH), 7.27 (2H, d, $J = 8.4$ Hz, CH), 7.52 (2H, d, $J = 8.4$ Hz, CH), 7.65 (2H, d, $J = 8.4$ Hz, CH), 7.69 (1H, s, CH), 7.89 (2H, d, $J = 8.4$ Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 128.7$, 128.8, 129.1, 130.1, 130.7, 131.2, 132.8, 134.7, 134.9, 135.4, 135.5, 139.7, 140.1, 142.4, 144.5, 144.8, 186.4 (C=O), 188.4 (C=O); Anal. Calcd for $C_{24}H_{13}Cl_3O_2S$ (471.78): C, 61.10; H, 2.78; S, 6.80%; found: C, 60.92; H, 2.69; S, 6.72%.

4.2.8. *2-Phenyl-4H-S,S-oxo-thiochromen-4-one* ***(6a)***

Red color semisolid; isolated yield 8%; IR (KBr): 3028, 1985, 1688, 1672, 1132, 1328, 880, 672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32$ (1H, td, $J = 8.4$ Hz, 1.8 Hz, CH), 7.54–7.59 (3H, m, CH), 7.64 (1H, t, $J = 7.5$ Hz, CH), 7.92 (1H, d, $J = 7.5$ Hz, CH), 8.14 (2H, d, $J = 7.2$ Hz, CH), 8.57 (1H, s, CH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 121.8$, 126.6, 127.3, 128.2, 128.5,

128.9, 131.2, 133.7, 136.4, 137.2, 144.9, 149.9, 189.3 (C=O), 192.1 (C=O); Anal. Calcd for $C_{24}H_{13}Cl_3O_2S$ (298.31): C, 64.42; H, 3.38; S, 10.75%; found: C, 6.29; H, 3.30; S, 10.62%; Mass m/e 316 ($M + H_2O$).

Acknowledgements

The authors thank DST, New Delhi, for assistance under the IRHPA program for providing funds for creating an NMR facility. Financial supports from CSIR-JRF, New Delhi, are gratefully acknowledged.

Note

1. Crystal data for 3b: Empirical formula $C_8H_7ClO_4$, Formula weight 202.59, triclinic, space group P-1, Unit cell = 5.8696(9) Å = 78.149(9)° b = 7.8565(12) Å, = 89.719(12)° c = 18.475(3) Å= 87.365(8)°, Volume 832.9(2) Å3, Z = 4, f(000) = 416, R(reflections) = 0.0311(1826), wR2(reflections) = 0.0783(2416), and Goodness-of-fit on F2 1.089. Complete crystallographic data, as a CIF file, have been deposited with the Cambridge Crystallographic Data Centre (CCDC number is 908749).

References

(1) (a) Sharpless, K.B.; Lauer, R.F. *J. Am. Chem. Soc.* **1972,** *94,* 7154–7155; (b) Arigoni, D.; Vasella, A.; Sharpless, K.B.; Jensen, H.P. *J. Am. Chem. Soc*. **1973,** *95,* 7917–7919; (c) Stephenson, L.M.; Speth, D.R. *J. Org. Chem*. **1979,** *44,* 4683–4689.
(2) (a) Shirude, S.T.; Patel, P. Giridhar, R.; Yadav, M.R. *Indian J. Chem.* **2006,** *45B,* 1080–1085; (b) Goswami, S.P.; Maity, A.C. *Chem. Lett.* **2007,** *36,* 1118–1119.
(3) Kariyone, K.; Yazawa, H. *Tetrahedron Lett.* **1970,** *11,* 2885–2888.
(4) Kovylyaeva, I.; Sharipova, R.R.; Strobykina, I.Y.; Militsina, O.I.; Musin, R.Z.; Beskrovnyi, D.V.; Gubaidullin, A.T.; Alfonsov, V.A.; Kataev, V.E. *Russ. J. Gen. Chem.* **2009,** *79,* 2663–2667.
(5) Lee, J.G.; Park, S.; Seo, J.W. *Bull. Korean Chem. Soc.* **1995,** *16,* 349–355.
(6) Kachanov, A.V.; Slabko, O.Y.; Baranova, O.V.; Shilova, E.V.; Kaminskii, V.A. *Tetrahedron Lett.* **2004,** *45,* 4461–4463.
(7) Bakulev, V.A.; Dehaen, W. *The Chemistry of 1,2,3-Thiadiazoles*; John Wiley & Sons, Inc.: New York, NY, 2004; pp. 193–228.
(8) Shaw, A.Y.; Denning, C.R.; Hulme, C. *Tetrahedron Lett*. **2012,** *53,* 4151–4153.
(9) (a) Cooper, A.J.L.; Ginos, J.Z.; Meister, A. *Chem. Rev*. **1983,** *83,* 321–536; (b) Mooney, B.P.; Miesnyk, J.P.; Randall, D.D. *Ann. Rev. Plant Biol.* **2002,** *53,* 357–375.
(10) Kerber, R.C.; Fernando, M.S. *J. Chem. Educ.* **2010,** *87,* 1079–1084.
(11) (a) Saravanan, S.; Azath, I.A.; Muthusubramanian, S. *J. Org. Chem.* **2008,** *73,* 2323–2329; (b) Saravanan, S.; Nithya, A.; Muthusubramanian, S. *J. Heterocycl. Chem.* **2006,** *43,* 149–155.
(12) Nagaraj, M.; Sathiyamoorthy, S.; Boominathan, M.; Muthusubramanian, S.; Bhuvanesh, N. *J. Heterocycl. Chem.*, in press, doi:10.1002/jhet.1557.
(13) Ravindran, G.; Nidhin, P.; Muthusubramanian, S.; Perumal, S. *J. Sulfur Chem.* **2008,** *29,* 575–581.
(14) Paul, N.; Shanmugam, M.J.; Muthusubramanian, S. *Synth. Commun*. **2013,** *43,* 129–138.
(15) (a) Aly, M.F.; Grigg, R. *Tetrahedron* **1988,** *44,* 7271–7282; (b) Corson, B.B.; Dodge, R.A.; Harris, S.A.; Hazen, R.K. *Org. Synth. Coll.* **1941,** *1,* 241–243.