

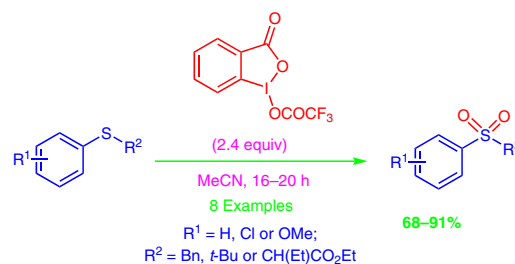
Oxidation of Organosulfides to Organosulfones with Trifluoromethyl 3-Oxo-1 λ^3 ,2-benziodoxole-1(3*H*)-carboxylate as an Oxidant

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Abstract An alternative approach is described for the oxidation of organosulfides to the corresponding organosulfones by using trifluoromethyl 3-oxo-1 λ^3 ,2-benziodoxole-1(3*H*)-carboxylate as an oxidant. The oxidation of the sulfides was performed by using 2.4 equivalents of the oxidant in refluxing acetonitrile. The oxidation products were isolated in good to excellent yields.

Key words oxidation, sulfides, sulfones, hypervalent iodine, oxidizing agents

Organosulfones are important scaffolds in medicinal¹ and natural-product chemistry.² The presence of a sulfone functionality makes these compounds more suitable as synthetic intermediates and as chemical building blocks for many biologically active compounds, for example **1–6** (Figure 1). Rofecoxib (Vioxx; **1**) has been introduced as a COX-2 inhibitor and is a potent anti-inflammatory drug³ and an analgesic.⁴ Laropiprant (**2**) is a prostaglandin D₂ receptor antagonist.⁵ Dapson (**3**) and sulfamethoxazole (**4**) have been developed as potent antibiotics for the treatment of leprosy and urinary infections, respectively.^{6,7} Glyburide (**5**) has been developed as a second-generation sulfonylurea, and is used in treating type 2 diabetes by enhancing insulin secretion.⁸ Carbutamide (**6**) is classed as a first-generation sulfonylurea, and is also used as an antidiabetic agent.⁹ In addition, various naturally occurring garlicnins isolated from *Allium sativum L.* have been shown to prevent cancer-cell growth.²

Numerous procedures have been developed for the oxidation of sulfides to sulfoxides and sulfones by various oxidants.^{10–12} In most of these approaches, oxidation of sulfides has been achieved by using various transition-metal

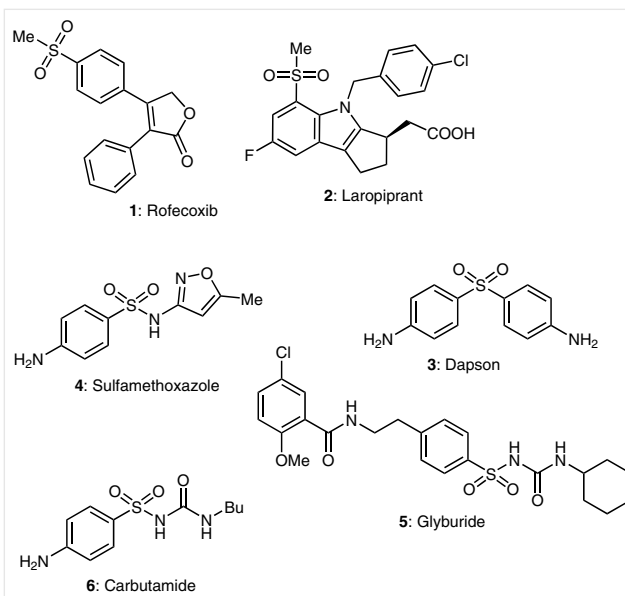
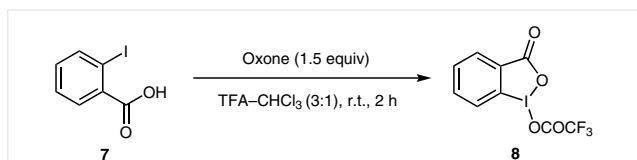


Figure 1 Structures of biologically active compounds **1–6** possessing a sulfone moiety

derivatives, including Ti,¹³ Sc,^{10b} Ru,¹⁴ Mn,¹⁵ Zr,¹⁶ Cu,¹⁷ or Fe¹⁸ complexes. In addition, several metal-free approaches have also been reported.^{19,20} Most oxidation approaches, however, involve the use of toxic metals or harsh reaction conditions. Recently, a synthesis of sulfones has been developed by using hypervalent iodine salts.²¹

In the past few decades, the chemistry of hypervalent iodine reagents has received attention due to their favorable safety profile and ease of handling.^{22,23} 1-Hydroxy-1 λ^3 ,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) is one of the most common hypervalent iodine reagents, and it has been used in various oxidation reactions.^{24,25} Despite being a versatile oxidant, IBX has several drawbacks, such as poor solu-

bility in common organic solvents²⁶ and a tendency to explode at elevated temperatures,²⁷ which limit its applications. We synthesized trifluoromethyl 3-oxo-1 λ^3 ,2-benziodoxole-1(3*H*)-carboxylate (**8**) by the oxidation of 2-iodobenzoic acid (**7**) with Oxone as oxidant in the presence of TFA (Scheme 1).²⁸ The synthesis of compound **8** has been reported previously,²⁹ but its oxidative properties are still unexplored.

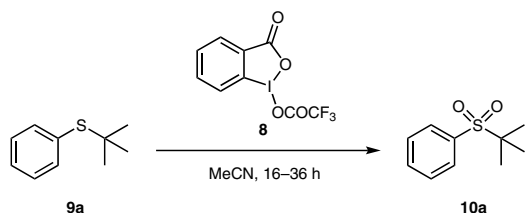


Scheme 1 Synthesis of trifluoromethyl 3-oxo-1 λ^3 ,2-benziodoxole-1(3*H*)-carboxylate (**8**) by the oxidation of 2-iodobenzoic acid (**7**).

Herein, we report the selective oxidation of sulfides **9** to the corresponding sulfones **10** by using benziodoxole **8** as an oxidant. The precursors **9a–c** were synthesized by the reaction of the corresponding thiophenols with *t*-butanol in the presence of an acid.^{30a} Other starting materials **9d–h** were synthesized by the reaction of thiophenols with alkyl bromides in the presence of sodium ethoxide.^{30b}

Initially, our efforts were directed at optimizing reaction conditions for the oxidation of *tert*-butyl phenyl sulfide (**9a**) as a model substrate. When the oxidation of sulfide **9a** was performed with 1.0 equivalents of benziodoxole **8** in acetonitrile at room temperature for 36 hours, the oxidation product **10a** was not obtained (Table 1, entry 1). When the same reaction was performed at the reflux temperature, conversion of the starting material was observed, and *tert*-butyl phenyl sulfide (**10a**) was obtained in 40% yield

Table 1 Optimization of the Stoichiometry of the Iodine(III) Reagent **8** for the Oxidation of Sulfide **9a** to Sulfone **10a**

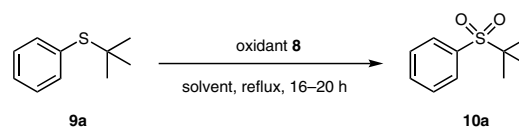


Entry	Reagent 8 (equiv)	Temp	Time (h)	Yield (%)
1	1.0	r.t.	36	–
2	1.0	reflux	24	40
3	1.5	reflux	24	56
4	2.0	reflux	16	80
5	2.4	reflux	16	85
6	3.0	reflux	16	86

(entry 2). The oxidation product **10a** was isolated in 56% yield when 1.5 equivalents of reagent **8** were used (entry 3). In this reaction, full conversion was not observed, and 40% of the starting material was recovered. When reactions were carried out by using 2.0 or 2.4 equivalents of **8**, product **10a** was obtained 80 and 85% yield, respectively (entries 4 and 5). When the reaction was performed with 3.0 equivalents of **8**, no significant improvement was observed, and **10a** was isolated in 86% yield (entry 6).

Next, our efforts were directed toward the optimization of the solvent. Various polar and nonpolar solvents were investigated for the oxidation of sulfide **9a** (Table 2). Initially, the oxidation was performed in MeCN, and oxidation product **10a** was isolated in 85% yield (Table 2, entry 1). The oxidation proceeded well in the polar aprotic solvents DMSO and dichloromethane, giving **10a** in 65 and 60% yield, respectively (entries 2 and 3). In the polar protic solvents methanol and ethanol, **10a** was obtained in 50 and 52% yield, respectively (Table 2, entries 4 and 5). When the oxidation was performed in THF or 1,3-dioxane, **10a** was obtained in 43 and 30% yield, respectively (entries 6 and 7). Therefore, the use of 2.4 equivalents of **8** in acetonitrile at the reflux for 16 hours was concluded to be optimal for the oxidation of sulfide **9a** to the corresponding sulfone **10a**.

Table 2 The Optimization of Solvent for the Oxidation of Sulfide **9a** to Sulfone **10a**

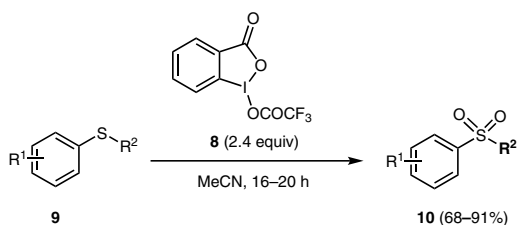


Entry	Solvent	Time (h)	Yield (%)
1	MeCN	16	85
2 ^a	DMSO	20	65
3	CH ₂ Cl ₂	20	60
4	MeOH	20	50
5	EtOH	20	52
6	THF	20	43
7	1,3-dioxane	20	30

^a The reaction was performed at 100 °C.

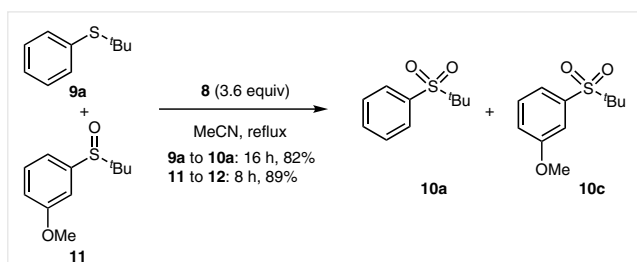
A series of sulfides **9b–h** was then successfully oxidized to the corresponding sulfones **10b–h** in 68–91% yield under the optimized conditions (Table 3, entries 1–8).³¹ All the oxidation reactions proceeded well, and both electron-withdrawing and electron-donating aromatic substituents were tolerated. The oxidation products were isolated in slightly better yields with substrates having electron-donating groups on the aromatic ring in comparison to substrates bearing electron-withdrawing groups.

Table 3 Oxidation of Sulfides 9b–h



Entry	R ¹	R ²	Time (h)	Product	Yield (%)
1	H	<i>t</i> -Bu	16	10a	85
2	4-Cl	<i>t</i> -Bu	20	10b	75
3	3-MeO	<i>t</i> -Bu	17	10c	89
4	H	Bn	16	10c	86
5	4-Cl	Bn	20	10e	81
6	3-MeO	Bn	16	10f	91
7	H	CH(Et)CO ₂ Et	16	10g	75
8	4-Cl	CH(Et)CO ₂ Et	18	10h	68

Next, we examined the selectivity of **8** towards the oxidation of sulfoxides and sulfides. To check the selectivity, a competitive reaction was performed between sulfide **9a** and sulfoxide **11** in acetonitrile at the reflux temperature. Sulfoxide **11** was synthesized by the oxidation of sulfide **9c** with *m*-CPBA at low temperature.³² Sulfide **9a** was oxidized to the corresponding sulfone **10a** in 16 hours, whereas the oxidation of sulfoxide **11** to sulfone **10c** was completed in eight hours. After the purification, sulfone **10a** was isolated in 82% yield, and sulfone **10c** was obtained in 89% yield (Scheme 2). The results of the competitive reaction suggest that reagent **8** can be used for the oxidation of either sulfides or sulfoxides to sulfones, but the oxidation of sulfoxides is selective over that of sulfides.

Scheme 2 Competitive oxidation of sulfide **9a** and sulfoxide **11** by using reagent **8**

In conclusion, we have developed an alternative approach for the oxidation of organosulfides to the corresponding organosulfones by using trifluoromethyl 3-oxo-1λ³,2-benziodoxole-1(3*H*)-carboxylate as an oxidant. This is the first report of the use of this compound as an oxidant.

Acknowledgements

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588575>.

References and Notes

- (a) Xu, F.; Chen, Y.; Fan, E.; Sun, Z. *Org. Lett.* **2016**, *18*, 2777. (b) Hartz, R. A.; Arvanitis, A. G.; Arnold, C.; Rescinito, J. P.; Hung, K. L.; Zhang, G.; Wong, H.; Langley, D. R.; Gilligan, P. J.; Trainor, G. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 934. (c) Pal, M.; RaoVeeramaneni, V.; Nagabelli, M.; RaoKallede, S.; Misra, P.; RaoCasturi, S.; Rao Veleswarapu, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1639. (d) Otzen, T.; Wempe, E. G.; Kunz, B.; Bartels, R.; Lehwerk-Yvetot, G.; Hänsel, W.; Schaper, K.-J.; Seydel, J. K. *J. Med. Chem.* **2003**, *47*, 240. (e) Doherty, G. A.; Kamenecka, T.; McCauley, E.; Van Riper, G.; Mumford, R. A.; Tong, S.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 729.
- Nohara, T.; Fujiwara, Y.; Ikeda, T.; Murakami, K.; Ono, M.; Nakano, D.; Kinjo, J. *Chem. Pharm. Bull.* **2013**, *61*, 695.
- Sang, Y.; Connor, D. T.; Doubleday, R.; Sorenson, R. J.; Sercel, A. D.; Unangst, P. C.; Roth, B. D.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem.* **1999**, *42*, 1151.
- Tozkoparan, B.; Küpeli, E.; Yeşilada, E.; Ertan, M. *Bioorg. Med. Chem.* **2007**, *15*, 1808.
- (a) Zhou, H.; Zhu, Q.; Gan, Z.; Dong, G.; Xu, Y. *Med. Chem. Res.* **2015**, *24*, 3920. (b) Sturino, F. C.; Neill, O. G.; Lachance, N.; Boyd, M.; Berthelette, C.; Labelle, M.; Li, L.; Roy, B.; Scheiget, J.; Tsou, N.; Aubin, Y.; Bateman, K. P.; Chaurat, N.; Day, S. H.; Levesque, J.-F.; Seto, C.; Silva, J. H.; Trimble, L. A.; Carriere, M.-C.; Denis, D.; Greig, G.; Kargman, S.; Lamontagne, S.; Matheiu, M.-C.; Sawyer, N.; Slipetz, D.; Abraham, W. M.; Jones, T.; McAuliffe, M.; Piechuta, H.; Nicoll-Griffith, D. A.; Wang, Z.; Zamboni, R.; Young, R. N.; Metters, K. M. *J. Med. Chem.* **2007**, *50*, 794.
- Yazdanyar, S.; Boer, J.; Ingvarsson, G.; Szepietowski, J. C.; Jemec, G. B. E. *Dermatology (Basel, Switz.)* **2011**, *222*, 342; DOI: 10.1159/000329023.
- Sunduru, N.; Salin, O.; Gylfe, A.; Elofsson, M. *Eur. J. Med. Chem.* **2015**, *101*, 595; and references cited therein.
- Zhao, J.; Li, Z.; Song, S.; Wang, M.-A.; Fu, B.; Zhang, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 5545; and references cited therein.
- El-Kerdawy, M. M.; Selim, H. A. *J. Drug Res.* **1973**, *5*, 135.
- (a) Sharipov, A. K. *Russ. J. Appl. Chem.* **2003**, *76*, 108; DOI: 10.1023/A:1023308303. (b) Matteucci, M.; Bhalay, G.; Bradley, M. *Org. Lett.* **2003**, *5*, 235.
- Sun, J.; Zhu, C.; Dai, Z.; Yang, M.; Pan, Y.; Hu, H. *J. Org. Chem.* **2004**, *69*, 8500.
- Mba, M.; Prins, L. J.; Licini, G. *Org. Lett.* **2007**, *9*, 21.
- (a) Gao, J.; Guo, H.; Liu, S.; Wang, M. *Tetrahedron Lett.* **2007**, *48*, 8453. (b) Khedher, I.; Ghorbel, A. *J. Porous Mater.* **2010**, *17*, 501.
- Li, T.-T.; Li, F.-M.; Zhao, W.-L.; Tian, Y.-H.; Chen, Y.; Cai, R.; Fu, W.-F. *Inorg. Chem.* **2015**, *54*, 183.
- Bagherzadeh, M.; Latifi, R.; Tahsini, L.; Amini, M. *Catal. Commun.* **2008**, *10*, 196.

- (16) Bonchio, M.; Licini, G.; Di Furia, F.; Mantovani, S.; Modena, G.; Nugent, W. A. *J. Org. Chem.* **1999**, *64*, 1326.
- (17) Liu, R.; Wu, L.-z.; Feng, X.-m.; Zhang, Z.; Li, Y.-z.; Wang, Z.-l. *Inorg. Chim. Acta* **2007**, *360*, 656.
- (18) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 8940.
- (19) Wagh, R. B.; Nagarkar, J. M. *Catal. Lett.* **2017**, *147*, 181.
- (20) Rostami, A.; Navasi, Y.; Moradi, D.; Ghorbani-Choghamarani, A. *Catal. Commun.* **2014**, *43*, 16.
- (21) (a) Umierski, N.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 188. (b) Margraf, N.; Manolikakes, G. *J. Org. Chem.* **2015**, *80*, 2582.
- (22) (a) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328. (b) Singh, F. V.; Wirth, T. In *Comprehensive Organic Synthesis II*; Knochel, P.; Molander, G. A., Eds.; Elsevier: Amsterdam, **2014**, 880. (c) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185. (d) Merritt, E. A.; Olofsson, B. *Angew. Chem.* **2009**, *121*, 9214; *Angew. Chem. Int. Ed.* **2009**, *48*, 9052. (e) Zhdankin, V. V. *ARKIVOC* **2009**, (i), 1. (f) Farooq, U.; Shah, A. A.; Wirth, T. *Angew. Chem.* **2009**, *121*, 1036; *Angew. Chem. Int. Ed.* **2009**, *48*, 1018. (g) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (h) Ladziata, U.; Zhdankin, V. V. *Synlett* **2007**, 527. (i) Wirth, T. *Angew. Chem.* **2005**, *117*, 3722; *Angew. Chem. Int. Ed.* **2005**, *44*, 3656. (j) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (k) Wirth, T. In *Organic Synthesis Highlights V*; Schmalz, H.-G.; Wirth, T., Eds.; Wiley-VCH: Weinheim, **2003**, 144. (l) Wirth, T. *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Springer: Berlin, **2003**. (m) Zhdankin, V. V. *Chem. Rev.* **2002**, *102*, 2523. (n) Wirth, T. *Angew. Chem.* **2001**, *113*, 2893; *Angew. Chem. Int. Ed.* **2001**, *40*, 2812.
- (23) (a) Qian, G.; Liu, B.; Tan, Q.; Zhang, S.; Xu, B. *Eur. J. Org. Chem.* **2014**, 4837. (b) Mizar, P.; Wirth, T. *Angew. Chem.* **2014**, 6103; *Angew. Chem. Int. Ed.* **2014**, *53*, 5993. (c) Singh, F. V.; Wirth, T. *Synthesis* **2013**, *45*, 2499; and references are cited therein. (d) Singh, F. V.; Rehbein, J.; Wirth, T. *ChemistryOpen* **2012**, *1*, 245. (e) Kajiyama, D.; Saitoh, T.; Yamaguchi, S.; Nishiyama, S. *Synthesis* **2012**, *44*, 1667. (f) Paz, N. R.; Santana, A. G.; Francisco, C. G.; Suárez, E.; González, C. C. *Org. Lett.* **2012**, *14*, 3388. (g) Wardrop, D. J.; Yermolina, M. V.; Bowen, E. G. *Synthesis* **2012**, *44*, 1199. (h) Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504. (i) Du, X.; Chen, H.; Chen, Y.; Chen, J.; Liu, Y. *Synlett* **2011**, 1010. (j) Wang, H.; Fan, R. *J. Org. Chem.* **2010**, *75*, 6994. (k) Moriarty, R. M.; Tyagi, S.; Kinch, M. *Tetrahedron* **2010**, *66*, 5801. (l) Bose, S. S.; Idrees, M. *Synthesis* **2010**, 398. (m) Pardo, L. M.; Tellitu, I.; Domínguez, E. *Synthesis* **2010**, 971.
- (24) (a) Xie, A.; Zhou, X.; Feng, L.; Hu, X.; Dong, W. *Tetrahedron* **2014**, *70*, 3514. (b) Xu, S.; Itto, K.; Satoh, M.; Arimoto, H. *Chem. Commun.* **2014**, *50*, 2758.
- (25) Matassini, C.; Parmeggiani, C.; Cardona, F.; Goti, A. *Org. Lett.* **2015**, *17*, 4082.
- (26) CAUTION! IBX and Dess–Martin periodinane are explosive upon impact or heating at >200 °C; see: Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, *68*, 3DOI: 10.1021/cen-v068n029.p002.
- (27) (a) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183. (c) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.
- (28) Zagulyaeva, A. A.; Yusubov, M. S.; Zhdankin, V. V. *J. Org. Chem.* **2010**, *75*, 2119.
- (29) (a) Kasumov, T. M.; Brel, V. K.; Grishin, Y. K.; Zefirov, N. S.; Stang, P. J. *Tetrahedron* **1997**, *53*, 1145. (b) Page, T. K.; Wirth, T. *Synthesis* **2006**, 3153.
- (30) (a) Freudendahl, D. M.; Iwaoka, M.; Wirth, T. *Eur. J. Org. Chem.* **2010**, 3934. (b) O'Mahony, G. E.; Ford, A.; Maguire, A. R. *J. Org. Chem.* **2012**, *77*, 3288.
- (31) **Sulfones 10a–h; General Procedure**
A mixture of the appropriate sulfide **9** (0.5 mmol) and benzodioxole **8** (413 mg, 2.4 equiv) in MeCN (3 mL) was refluxed for 16–20 h. When the reaction was complete (TLC), sat. aq NaHCO₃ (5 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated under vacuum. The crude product was purified by column chromatography [silica gel, EtOAc–hexane (1:3)].
tert-Butyl Phenyl Sulfone (10a)^{22b}
White solid; yield: 84 mg (0.42 mmol, 85%); mp: 90–92 °C. IR (film): 697, 725, 749, 764, 802, 996, 1021, 1076, 1130, 1277, 1294, 1449, 1475 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 1.23 (s, 9 H, *t*-Bu), 7.46 (t, *J* = 7.6 Hz, 2 H, ArH), 7.56 (t, *J* = 7.6 Hz, 1 H, ArH), 7.77 (d, *J* = 7.6 Hz, 2 H, ArH). ¹³C NMR (100 MHz, CDCl₃): δ = 23.5, 59.7, 128.7, 130.3, 133.6, 135.2. GC/MS: *m/z* (%) = 198(5), 143(25), 79(13), 77(50), 58(29), 57(100), 51(51), 41(50).
- (32) Mangaonkar, S. R.; Singh, F. V. *Der Pharma Chem.* **2016**, *8*, 419.