Research Article

Oxidative Cleavage of β -Keto Sulfones via Nitrous Acid

Hatem A. Abdel-Aziz^{1,2}

¹Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

²Department of Applied Organic Chemistry, National Research Center, Dokki, Cairo 12622, Egypt

Correspondence should be addressed to Hatem A. Abdel-Aziz; hatem_741@yahoo.com

Received 27 October 2014; Accepted 29 November 2014; Published 15 December 2014

Academic Editor: Gustavo Portalone

Copyright © 2014 Hatem A. Abdel-Aziz. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The reaction of nitrous acid with 1-aryl-2-(arylsulfonyl)ethanones **3a–e** afforded the unexpected arenecarboxylic acids **12a–e**, formic acid **14**, and benzene/4-toluenesulfinic acid **15a, b** through oxidative cleavage reaction. 4-Chlorobenzoic acid (**12a**), [1,1'-biphenyl]-4-carboxylic acid (**12b**), 2-naphthoic acid (**12c**), 2-thiophenecarboxylic acid (**12d**), and 2-benzofurancarboxylic acid (**12e**) were isolated in 72%, 62%, 55%, 58%, and 62% yields, respectively. The reported mechanistic pathways proposed the production of 1-aryl-2-(phenyl/tolylsulfonyl)ethane-1,2-dione **7** instead of arenecarboxylic acids **12**. A mechanistic pathway to explain the reaction of nitrous acid with 1-aryl-2-(arylsulfonyl)ethanones **3a–e** was suggested. In this pathway, the intermediate 1,2-oxazete **10** lost benzene/4-toluenesulfinic acid **15** to produce 1,2-oxazet-3-one **11**. Ring cleavage of the latter intermediate afforded the arenecarboxylic acids **12**.

1. Introduction

β -Keto sulfones are versatile synthetic intermediates used for the preparation of diverse classes of organic compounds such as substituted acetylenes, olefins, allenes, vinylenes, and pyrans. The chemistry of β -keto sulfones achieved a significant peak of interest during the last decades and nowadays constitutes a whole branch of organosulfur chemistry [1–3]. Although the chemistry of β -keto sulfones has been widely investigated, little has appeared in the literature concerning their oximes. Oximes represent an important class of organic compounds with a wide range of practical applications. Oximes can be synthesized by condensation of an aldehyde or a ketone with hydroxylamine. They can also be obtained from reaction of nitrites with active methylene compounds. The latter reaction produces C-nitroso compounds which usually rearrange to oximino compounds. This reaction has value as a means of introducing an oximino group in a part of molecule that does not have a carbonyl group for direct oximation [4]. The oxidation of oximes with various inorganic acids is a known procedure for the recovery of aldehydes and ketones from their corresponding oximes [5]. This method has been widely utilized and its reaction mechanism has been reported [6]. In this study and in continuation of our interest in chemistry

of β -keto sulfones [7–9], we shall deal with the reaction of nitrous acid with β -keto sulfones **3** and therefore the probable modes of formation of the corresponding carboxylic acids **12**.

2. Experimental

2.1. Chemistry

2.1.1. General. Melting points were determined on a Galenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded as KBr disks using the Perkin Elmer FT-IR Spectrum BX apparatus. NMR spectra were scanned in DMSO-*d*₆ on a Bruker NMR spectrometer operating at 500 MHz for ¹H and 125 MHz for ¹³C. Chemical shifts are expressed in δ -values (ppm) relative to TMS as an internal standard. Coupling constants (*J*) are expressed in Hz. D₂O was added to confirm the exchangeable protons. The mass spectra were performed using a Varian MAT CH-5 spectrometer (70 eV).

2.1.2. Synthesis of 1-Aryl-2-arylsulfonyl Ethanones 3a–f. These compounds were prepared according to the reported method [10–15].

FIGURE 1: The reaction of nitrous acid with β -keto sulfones **3a-e**.

2.1.3. Synthesis of Oximes 4a-f. To a stirred cold solution of β -keto sulfones **3a-f** [10–15] (10 mmol) in glacial acetic acid (20 mL), sulfuric acid (1 mL, 50%) was added. Then cold solution of sodium nitrite (0.7 g, 10 mmol) in water (5 mL) was added dropwise with stirring at such a rate that the temperature remains in the range 0–5°C. Over a period of 30 min, a light blue solution of nitrous acid is produced. The mixture is stirred for extra 1 h at 25°C. The reaction mixture was poured into cold water and the solid product was filtered off, washed with water, and dried. Recrystallization from EtOH afforded **4a-f** which were used without any further purification in the next step.

2.1.4. The Reaction of Nitrous Acid with β -Keto Sulfones 3a-e. To a stirred cold solution of β -keto sulfones **3a-e** (10 mmol) or oximes **4a-e** (10 mmol) in glacial acetic acid (30 mL), sulfuric acid (5 mL, 50%) was added. Then cold solution of sodium nitrite (2.1 g, 30 mmol) in water (10 mL) was added dropwise with stirring at such a rate that the temperature remains in the range 0–5°C. Over a period of 30 min, a light blue solution of nitrous acid is produced. The mixture is stirred for extra 48 h at 25°C. The solid that precipitated was collected, washed with water, and dried. Recrystallization from EtOH afforded the corresponding carboxylic acids **12a-e** in 55–72% yield. Formic acid (**14**) and benzene/4-toluenesulfinic acid **15** were detected in filtrate using chromatographic analyses. 4-Chlorobenzoic acid (**12a**) was isolated in 65% yield by the reaction of 1-(4-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]ethanone (**3f**) instead of **3a**.

(1) **4-Chlorobenzoic Acid (12a).** This acid was prepared from 1-(4-chlorophenyl)-2-(phenylsulfonyl)ethanone (**3a**) [10] in 65% yield (1.02 g). 1-(4-Chlorophenyl)-2-[(4-methylphenyl)sulfonyl]ethanone (**3f**) [11] afforded 1.13 g (72% yield) of 4-chlorobenzoic acid (**12a**); m.p. 238–240°C (Lit. m.p.

238–241°C) [16]; ^1H NMR δ 7.57 (d, J = 8.5 Hz, 2H, ArHs), 7.95 (d, J = 8.5 Hz, 2H, ArHs), 13.20 (s, D₂O exchangeable, 1H, OH); ^{13}C NMR δ 128.69 (C3 and C5), 129.72 (C1), 131.10 (C2 and C6), 137.70 (C4), 166.45 (C=O); MS (EI) m/z 156 [M^+], 157 [$\text{M}^+ + 1$], 158 [$\text{M}^+ + 2$].

(2) **[1,1'-Biphenyl]-4-carboxylic Acid (12b).** This acid was prepared from 1-(1,1'-biphenyl-4-yl)-2-(phenylsulfonyl)ethanone (**3b**) [12] in 62% yield (1.23 g); m.p. 225–227°C (Lit. m.p. 220–225°C) [17]; ^1H NMR δ 7.43 (t, J = 7.5 Hz, 1H, ArH), 7.51 (t, J = 7.5 Hz, 2H, ArHs), 7.75 (d, J = 7.5 Hz, 2H, ArHs), 7.79 (d, J = 8.5 Hz, 2H, ArHs), 8.03 (d, J = 8.5 Hz, 2H, ArHs), 13.00 (s, D₂O exchangeable, 1H, OH); ^{13}C NMR δ 126.70 (C3 and C5), 126.91 (C2 and C6), 128.20 (C4 and C4'), 129.04 (C3' and C5'), 129.90 (C2' and C6'), 139.07 (C1'), 144.0 (C1), 167.26 (C=O); MS (EI) m/z 198 [M^+].

(3) **2-Naphthoic Acid (12c).** This acid was prepared from 2-[(4-methylphenyl)sulfonyl]-1-(2-naphthalenyl)ethanone (**3c**) [13] in 55% yield (0.95 g); m.p. 186–188°C (Lit. m.p. 185–187°C) [18]; ^1H NMR δ 7.60–7.68 (m, 2H, ArHs), 7.98–8.03 (m, 3H, ArHs), 8.21 (d, J = 8.0 Hz, 1H, ArH), 8.62 (s, 1H, ArH), 13.11 (s, D₂O exchangeable, 1H, OH); ^{13}C NMR δ 125.25 (C3), 126.69 (C2), 127.60 (C7), 128.01 (C5), 128.14 (C4), 128.63 (C6), 129.20 (C8), 130.34 (C1), 132.14 (C8a), 134.80 (C4a), 167.56 (C=O); MS (EI) m/z 172 [M^+].

(4) **2-Thiophenecarboxylic Acid (12d).** This acid was prepared from 2-[(4-methylphenyl)sulfonyl]-1-(2-thienyl)ethanone (**3d**) [14] in 58% yield (0.74 g); m.p. 124–126°C (Lit. m.p. 125–127°C) [19]; ^1H NMR δ 7.19 (dd, J = 3.5, 4.8 Hz, 1H, H4), 7.727 (dd, J = 0.7, 3.5 Hz, 1H, H5), 7.91 (dd, J = 0.7, 4.8 Hz, 1H, H3), 13.23 (s, D₂O exchangeable, 1H, OH); ^{13}C NMR δ 135.20 (C2), 133.79 (C3), 128.82 (C4), 133.81 (C5), 163.51 (C=O); MS (EI) m/z 128 [M^+].

FIGURE 2: The reported mechanistic pathways A and B [6] for the reaction of nitrous acid with oximes suggested the formation of sulfonyl-diketone 7 during the reaction of nitrous acid with oxime 4. The proposed mechanistic pathway of the reaction of nitrous acid with β -keto sulfones 3 through intermediate 1,2-oxazete 10, pathway C.

(5) 2-Benzofurancarboxylic Acid (12e). This acid was synthesized from 1-(2-benzofuranyl)-2-(phenylsulfonyl)ethanone (3e) [15] in 52% yield (0.84 g); m.p. 193–195°C (Lit. m.p. 193–196°C) [20]; ^1H NMR δ 7.38 (t, $J = 7.5$ Hz, 1H, H5), 7.53 (t, $J = 7.5$ Hz, 1H, H4), 7.71–7.77 (m, 2H, H3+H4), 7.83 (d, $J = 7.5$ Hz, 1H, H6), 13.80 (s, D_2O exchangeable, 1H, OH); ^{13}C NMR δ 114.35 (C8), 115.82 (C3), 123.00 (C4), 123.91 (C5), 127.04 (C6), 127.84 (C3a), 146.02 (C2), 154.95 (C8a), 160.02 (C=O); MS (EI) m/z 162 [M^+].

3. Results and Discussion

β -Keto sulfones 3a–e were synthesized by the reaction of 2-bromo-1-arylethanone 1a–e with the appropriate sodium arylsulfate 2a, b according to the reported method [10–15]. Treatment of β -keto sulfones 3a–e with sodium nitrite, in acetic acid containing sulfuric acid, afforded the corresponding carboxylic acids 12a–e in addition to formic acid (14) and benzene/4-toluenesulfinic acid 15a, b (Figure 1).

Interestingly, it was found that this method provides the possibility to prepare carboxylic acids through the formation of oximes 4a–e as intermediates followed by the oxidative cleavage process of C–C bond by nitrous acid under the application of mild reaction conditions. In general, normal ketones are not oxidized except under extremely hard conditions and give several products [21].

4-Chlorobenzoic acid (12a), [1,1'-biphenyl]-4-carboxylic acid (12b), 2-naphthoic acid (12c), 2-thiophenecarboxylic

acid (12d), and 2-benzofurancarboxylic acid (12e) were isolated in 72%, 62%, 55%, 58%, and 62% yields, respectively, by the reaction of β -keto sulfones 3a–e with excess nitrous acid at 0–5°C. 4-Chlorobenzoic acid (12a) was isolated in 65% yield by the reaction of 1-(4-chlorophenyl)-2-[(4-methylphenyl)sulfonyl]ethanone (3f) instead of 3a. The structures of carboxylic acids 12a–e are assigned on the basis of their spectral data and physical constants which are identical with those described for authentic samples of 12a–e obtained commercially [16–20]. For example, ^1H NMR of acids 12a–e revealed the D_2O exchangeable signal of carboxylic OH in the region δ 13.0–13.8 whereas their ^{13}C NMR showed the signal due to the carbon of carbonyl function in the region δ 160.2–167.56. ^1H NMR of 12a showed the AB system of *Para* substituted benzene ring at δ 7.57 and 7.95 as two doublets with $J = 8.5$ Hz, whereas the ^1H NMR of 15d revealed three doublets of doublets (dd) signals at δ 7.19 ($J = 3.5, 4.8$ Hz), 7.727 ($J = 0.7, 3.5$ Hz), and 7.91 ($J = 0.7, 4.8$ Hz) for H4, H5, and H3 of thiophene moiety, respectively.

Mechanistic explanation has been reported for the reaction of nitrous acid and nitrosonium ion NO^+ with oximes by Kliegman and Barnes [6]. They proposed two mechanistic pathways using ^{15}N nitrous acid to determine the reaction products. The intermediate product of the reaction of nitrous acid with oxime 4 is the iminoxyl cation 5 which can react in one of these two pathways A or B (Figure 2).

The nitrosating agent nitrous acid is formed *in situ* by the action of acetic or mineral acid on sodium nitrite and

a further reaction takes place to give the nitrosonium ion NO^+ (Figure 2). The reported mechanistic pathways through hydrolysis of iminoxyl cation **5** to give hydroxy precursor **6** (pathway A) or through nitrosation of **5** to give intermediate **8** and then 1,2,3-oxadiazete **9** (pathway B) proposed the production of 1-aryl-2-(phenyl/tolylsulfonyl)ethane-1,2-dione **7** instead of arenecarboxylic acids **12** (Figure 2).

These results stimulate our interest to offer a mechanistic pathway (pathway C) to explain the formation of acids **12** as main reaction products through oxidative cleavage of β -keto sulfone oximes **4**, keeping in mind the formation of formic acid (**14**) and benzene/4-toluenesulfinic acid **15** (Figure 2). In this pathway, hydroxy precursor **6** cyclized to give the intermediate 1,2-oxazete **10** which lost benzene/4-toluenesulfinic acid **15** to produce 1,2-oxazet-3-one **11**. Ring cleavage of the latter intermediate afforded the arenecarboxylic acids **12** and di-anion **13** [6] which reacted with water to give formic acid (**14**).

4. Conclusion

In conclusion, we studied the reaction of nitrous acid with β -keto sulfones **3a–e**, and we also proposed a mechanistic pathway to explain the formation of unexpected carboxylic acids **12a–e** through the oxidative cleavage reaction.

Conflict of Interests

The author has declared that there is no conflict of interests.

Acknowledgment

The author would like to extend his sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group Project no. RGP-VPP-321.

References

- [1] Y. M. Markitanov, V. M. Timoshenko, and Y. G. Shermolovich, " β -Keto sulfones: preparation and application in organic synthesis," *Journal of Sulfur Chemistry*, vol. 35, no. 2, pp. 188–236, 2014.
- [2] R. E. Swenson, T. J. Sowin, and H. Q. Zhang, "Synthesis of substituted quinolines using the dianion addition of *N*-Boc-anilines and α -tolylsulfonyl- α,β -unsaturated ketones," *The Journal of Organic Chemistry*, vol. 67, no. 26, pp. 9182–9185, 2002.
- [3] J. E. Baldwin, R. M. Adlington, N. P. Crouch, R. L. Hill, and T. G. Laffey, "An expedient synthesis of trisubstituted allenes," *Tetrahedron Letters*, vol. 36, no. 43, pp. 7925–7928, 1995.
- [4] S. R. Sandler and W. Karo, *Organic Functional Group Preparations*, vol. 3, Academic Press, 2nd edition, 1989.
- [5] N. Quan, X.-X. Shi, L.-D. Nie, J. Dong, and R.-H. Zhu, "A green chemistry method for the regeneration of carbonyl compounds from oximes by using cupric chloride dihydrate as a recoverable promoter for hydrolysis," *Synlett*, vol. 1642, pp. 1028–1032, 2011.
- [6] J. M. Kliegman and R. K. Barnes, "The reaction of nitrous acid with oximes," *Journal of Organic Chemistry*, vol. 37, no. 25, pp. 4223–4225, 1972.
- [7] H. A. Abdel-Aziz, K. A. Al-Rashood, K. E. H. Eltahir, and G. M. Suddek, "Synthesis of *N*-benzenesulfonamide-1*H*-pyrazoles bearing arylsulfonyl moiety: novel celecoxib analogs as potent anti-inflammatory agents," *European Journal of Medicinal Chemistry*, vol. 80, pp. 416–422, 2014.
- [8] H. A. Abdel-Aziz, H. A. Ghabbour, M. A. Bhat, and H.-K. Fun, "Microwave-assisted synthesis and characterization of certain oximes, hydrazones and olefins derived from β -keto sulfones," *Journal of Chemistry*, vol. 2014, Article ID 532467, 6 pages, 2014.
- [9] H. A. Abdel-Aziz, "Method for the preparation of carboxylic acids," European Patent, patent application pending no. EP 14163967.7, 2014.
- [10] X. Wan, Q. Meng, H. Zhang, Y. Sun, W. Fan, and Z. Zhang, "An efficient synthesis of chiral β -hydroxy sulfones via Ru-catalyzed enantioselective hydrogenation in the presence of iodine," *Organic Letters*, vol. 9, no. 26, pp. 5613–5616, 2007.
- [11] N. Samakkanad, P. Katrun, T. Techajaroontit et al., "IBX/I2-Mediated reaction of sodium arenesulfinates with alkenes: facile synthesis of β -keto sulfones," *Synthesis*, vol. 44, no. 11, pp. 1693–1699, 2012.
- [12] D. Ruhlmann and J. P. Fouassier, "Relations structure-proprietés dans les photoamorceurs de polymérisation-8. les dérivés de sulfonyl cétones," *European Polymer Journal*, vol. 29, no. 8, pp. 1079–1088, 1993.
- [13] K. Kim, S. R. Mani, and H. J. Shine, "Ion radicals. XXXV. Reactions of thianthrene and phenoxathiin cation radicals with ketones. Formation and reactions of β -ketosulfonium perchlorates and ylides," *Journal of Organic Chemistry*, vol. 40, no. 26, pp. 3857–3862, 1975.
- [14] Y. Din, A. Fan, and Z. Zhang, "Synthesis of 2-(arylsulfonyl)-1-(2-thienyl)ethanones," *Yingyong Huaxue*, vol. 14, no. 3, pp. 113–114, 1997.
- [15] H. A. Abdel-Aziz, S. W. Ng, and E. R. T. Tiekink, "1-(1-Benzofuran-2-yl)-2-(phenylsulfonyl) ethanone," *Acta Crystallographica*, vol. E67, no. 10, Article ID o2675, 2011.
- [16] <https://www.sigmaaldrich.com/catalog/product/aldrich/135585>.
- [17] <https://www.sigmaaldrich.com/catalog/product/aldrich/b34729>.
- [18] <https://www.sigmaaldrich.com/catalog/product/aldrich/180246>.
- [19] <https://www.sigmaaldrich.com/catalog/product/aldrich/t32603>.
- [20] <https://www.sigmaaldrich.com/catalog/product/aldrich/307270>.
- [21] F. Adam, T.-S. Chew, and J. Andas, "Liquid phase oxidation of acetophenone over rice husk silica vanadium catalyst," *Chinese Journal of Catalysis*, vol. 33, no. 2-3, pp. 518–522, 2012.