NJC

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/d0nj05285j

One-pot access to sulfonylated naphthalenediols/hydroquinones from naphthols/phenols with sodium sulfinates in an aqueous medium†

Lingxin Meng,[a] Ruike Zhang,[a] Yuqiu Guan,[a] Tian Chen,[a] Zhiqiang Ding,[a] Gongshu Wang,[a] Aikebaier Reheman,*[b] Zhangpei Chen *[a] and Jianshe Hu [a]

Received 28th October 2020,
Accepted 25th November 2020

DOI: 10.1039/d0nj05285j

rsc.li/njc

A one-pot method towards sulfonylated hydroquinones/naphthalenediols in an aqueous medium has been developed with up to 97% yield. The whole reaction requiring no transition-metal catalysts could proceed smoothly with hypervalent iodine compounds as the oxidant. Both naphthols and phenols were viable with inexpensive and readily available sodium sulfinates as the sulfonylation reagents under an ambient atmosphere. This procedure is scalable, and the products could be easily obtained without column chromatography isolation.

Introduction

Naphthalenediol and hydroquinone derivatives are important structural motifs and omnipresent in many bioactive pharmaceuticals, agricultural drugs, dyestuffs, antioxidants, and materials.[1] Among them, the sulfone-containing hydroquinones have been found to possess potential pharmacological activities.[2] As depicted in Fig. 1, sulfone-containing hydroquinones 2-tosylnaphthalene-1,4-diol **A** and 2-tosylbenzene-1,4-diol **B** are potent inhibitors of β-Ketoacyl-ACP-synthase III (FabH), an essential condensing enzyme in bacterial fatty acid bio-synthesis.[3] The alkylsulfuryl diverged hydroquinone **C** is the inhibitor of coenzyme Q systems[4] and the quinoline based sulfones **D** exhibited good activities as liver X receptor agonists.[5]

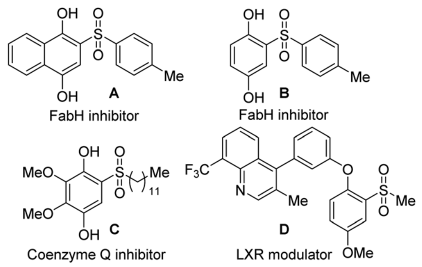


Fig. 1 Examples of bioactive sulfone-containing naphthalenediols and hydroquinones.

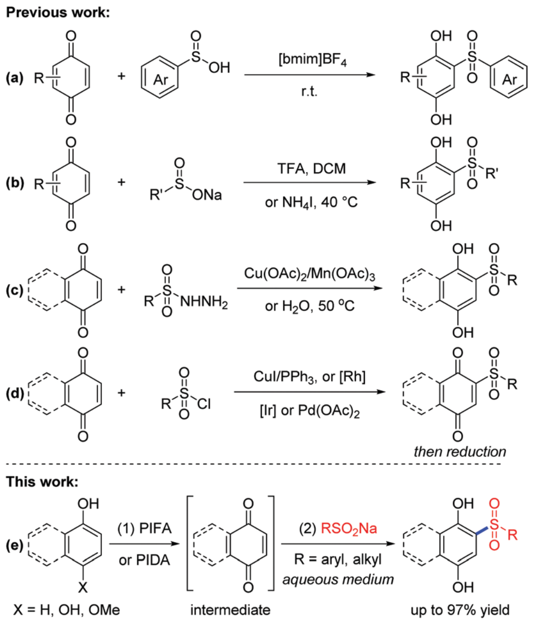
Consequently, the preponderance of sulfone-containing hydroquinones has expedited the exploration of reliable methods for their preparation.[6] Some classical approaches include oxidation of sulfides and electrophilic sulfonylation of arenes.[7] However, the limited substrate scope and tedious synthesis of the starting materials impeded their further applications. Subsequently, the method of conjugate addition of arylsulfinic acids to benzoquinones in ionic liquid solvents was developed by Yadav and co-workers (Scheme 1a).[8] Similarly, the addition reactions of arylsulfinic salts with benzoquinones were also achieved by using trifluoroacetic acid (TFA) or NH_4I as the promoter, respectively (Scheme 1b).[9,10] In 2017, the Wu group developed Cu and Mn synergistically facilitated sulfonylation of quinones with aryl(alkyl)sulfonyl hydrazides as the sulphur source (Scheme 1c).[11] In the same year, Wei and co-workers found that water and heat could also promote this transformation, providing the desired sulfonylated products with moderate to excellent yields.[12] Another approach was based on transition-metal-catalyzed C–H sulfonylation of quinones with copper, rhodium, palladium, and iridium as the catalyst and sulfonyl chloride as the sulphur source, and then followed by reduction (Scheme 1d).[12] Although these reported procedures are generally reliable, the development of more efficient and greener synthetic approaches to versatile sulfone-containing hydroquinones still remains highly desirable.

Considering that the quinones are generally obtained by oxidation of hydroquinones,[13] directly converting hydroquinones into the corresponding sulfonylated hydroquinones in one-step would provide an efficient, step-economic and attractive protocol for these compounds. Herein, we report our findings toward the construction of various sulfonylated naphthalenediols and hydroquinones from naphthols or phenols with sodium sulfinates in an aqueous medium (Scheme 1e).

---

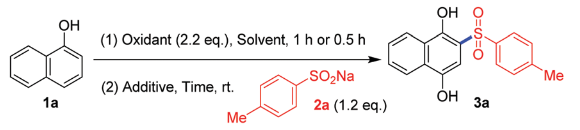
[a] *Center for Molecular Science and Engineering, College of Sciences, Northeastern University, Shenyang 110819, P. R. China. E-mail: chenzhangpei@mail.neu.edu.cn*
[b] *Key Laboratory of Toxicology, Medical College, Ningde Normal University, Ningde, 352100, China. E-mail: akbarphd@126.com*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0nj05285j



Scheme 1 Synthetic strategies for sulfonylated naphthalenediols or hydroquinones.

Table 1 Condition optimization



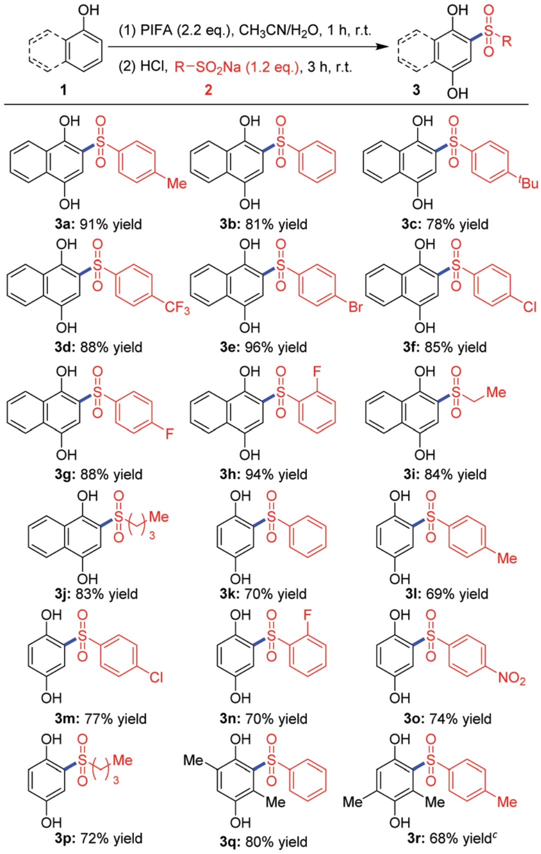
Entry[a]	Oxidant	Solvent	Additive	Time (h)	Yield[b] (%)
1	PIDA	H_2O	—	1	28
2	PIDA	MeOH : H_2O = 2 : 1	—	1	50
3	PIDA	DCM : H_2O = 2 : 1	—	1	22
4	PIDA	DMSO : H_2O = 2 : 1	—	1	37
5	PIDA	CH_3CN : H_2O = 2 : 1	—	1	76
6	PIDA	CH_3CN : H_2O = 1 : 1	—	1	70
7	PIDA	CH_3CN : H_2O = 1 : 2	—	1	68
8[c]	PIDA	CH_3CN : H_2O = 2 : 1	—	1	66
9	*m*-CPBA	CH_3CN : H_2O = 2 : 1	—	1	20
10	PIFA	CH_3CN : H_2O = 2 : 1	—	1	80
11	H_2O_2	CH_3CN : H_2O = 2 : 1	—	1	N.R.
12	$K_2S_2O_8$	CH_3CN : H_2O = 2 : 1	—	1	N.R.
13	TBHP	CH_3CN : H_2O = 2 : 1	—	1	N.R.
14	PIFA	CH_3CN : H_2O = 2 : 1	—	5	82
15	PIFA	CH_3CN : H_2O = 2 : 1	CH_3COOH	3	89
16	PIFA	CH_3CN : H_2O = 2 : 1	TFA	3	89
17	PIFA	CH_3CN : H_2O = 2 : 1	TsOH	3	89
18	PIFA	CH_3CN : H_2O = 2 : 1	Et_3N	3	80
19	PIFA	CH_3CN : H_2O = 2 : 1	$NaHCO_3$	3	74
20	PIFA	CH_3CN : H_2O = 2 : 1	HCl (aqua.)	3	91
21[d]	PIFA	CH_3CN : H_2O = 2 : 1	HCl (aqua.)	3	85

[a] Reaction conditions: **1a** (0.30 mmol), oxidant (0.66 mmol, 2.2 equiv.), and solvent (3.0 mL) were added to a flask and stirred at room temperature for 1 h under air; then the additive (0.30 mmol, 1.0 equiv.) and **2a** (0.36 mmol, 1.2 equiv.) were added, and the mixture was stirred for another certain time to generate the product. [b] Isolated yields after column chromatography; N.R. means no reaction. [c] **1a**, **2a**, solvent and the oxidant were added together and the mixture was stirred for 4 h. [d] Reaction time of the oxidation process (step 1) was reduced to 0.5 h.

Results and discussion

Our initial study began with the sulfonylation reaction between the 1-naphthalenol **1a** and sodium 4-methylbenzenesulfinate **2a** as model substrates to optimize the reaction conditions (Table 1). The easy available and widely used (diacetoxyiodo)benzene (PIDA) was selected as the *in situ* oxidant to facilitate the one-pot reaction. As shown in entry 1, when we mixed **1a** and PIDA in water for 1 h first, then added 1.2 equivalent of **2a** to the mixture and stirred the reaction for another hour, the desirable product **3a** was obtained with 28% isolated yield. Subsequently, we carefully studied the solvent effects on the yields, including the mixture solvents of methanol (MeOH), dichloromethane (DCM), dimethylsulfoxide (DMSO) and acetonitrile with water (entries 2–5). To our delight, with the employment of CH_3CN/H_2O (volume ratio 2 : 1) as the reaction medium, the reaction could proceed smoothly, providing **3a** with 76% yield. However, further altering the volume ratio of acetonitrile and water failed to promote the yield (entries 6 and 7). It is worth mentioning that subjecting the substrates with PIDA in one portion to the solvent and stirring the mixture for 4 h could also obtain the desired product with a slightly lower yield of 66% (entry 8). Then, we investigated the effect of other oxidants on the yield of this sulfonylation, including 3-chloroperoxybenzoic acid (*m*-CPBA), [bis(trifluoroacetoxy)iodo]benzene (PIFA), H_2O_2, $K_2S_2O_8$ and *tert*-butyl hydroperoxide (TBHP), and the PIFA showed the best result of 80% yield (entries 9–13). Disappointingly, prolongation of the reaction time failed to increase the yield, and this may be attributed to the favouring of side reactions according to the previous results (entry 14).[14] Documents have demonstrated that acids or bases could promote sulfonylation reactions;[9,15] therefore, we turned our attention to evaluating the effects of various additives (entries 15–20). After a systematic screening, the commonly used hydrochloric acid was proven as the best choice, providing **3a** with 91% yield (entry 20). Notably, reducing the oxidation process to 0.5 h, the yield decreased slightly, providing **3a** in 85% yield (entry 21). Thus, the optimized reaction conditions were established as **1a** (1.0 equiv.), PIFA (2.2 equiv.) and CH_3CN/H_2O = 2 : 1 (3.0 mL), stirred for 1 h first and then aqueous HCl (1.0 equiv.) and **2a** (1.2 equiv.), stirred for another 3 h at room temperature.

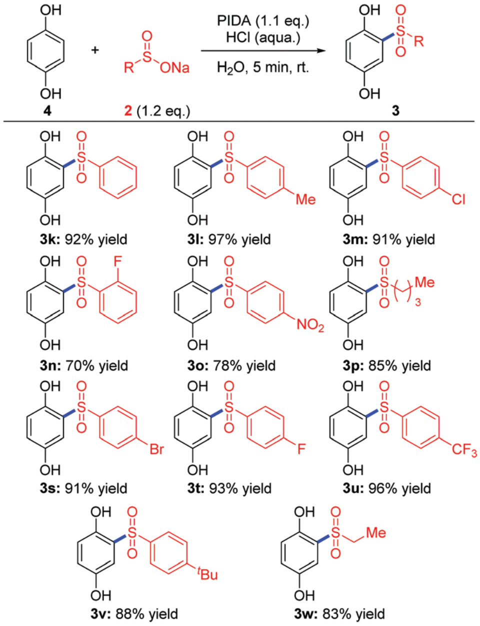
After establishing the optimal conditions, we examined the substrate scope of this sulfonylation reaction and the results are summarized in Scheme 2. Gratifyingly, a variety of sodium arylsulfinates were smoothly coupled to the 1-naphthalenol scaffold, delivering the corresponding sulfonylated naphthalenediols in 78–96% yields (**3a–h**). Various substituents on the phenyl group of sodium arylsulfinate are tolerated in this reaction, including tertiary butyl, trifluoromethyl, and halogen. The electronic properties of the substituted groups in the phenyl group of sodium arylsulfinates had little effect on the reactivity and a phenyl group bearing an *ortho*-fluorine atom was also tolerated giving 94% isolated yield (**3h**). It was noted that the sulfonylation reaction with alkyl substituted sodium sulfinates also occurred with high yields (**3i–j**). Significantly, the sulfonylation of various phenols was also viable (**3k–r**). For phenols, the scope of sodium arylsulfinates, including phenyl groups bearing various electron-donating groups or electron-withdrawing substituents, proved to be broad, and all of the



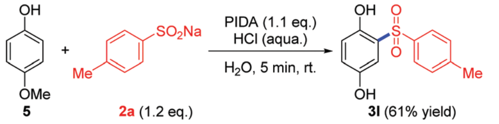
Scheme 2 Substrate scope of one-pot sulfonylation reactions[a,b]. [a]Reaction conditions: phenols **1** (0.30 mmol), PIFA (0.66 mmol), $CH_3CN:H_2O$ = 2 : 1 (3.0 mL), r.t., air, 1 h, and then aqueous HCl (0.30 mmol), sodium sulfinate **2** (0.36 mmol), r.t., air, 3 h. [b] Isolated yields after column chromatography. [c] 4.0 equiv. of sodium 4-methylbenzenesulfinate **2a**, 80 °C.

corresponding products were isolated in 68–77% yields. Notably, the nitro group remained intact in this reaction, leading to the sulfonylated product **3o** with 74% yield. In addition, the transformation with alkyl substituted sodium sulfinate also worked well, affording the desired product in 72% yield (**3p**). Moreover, dimethyl substituted phenol 2,5-dimethylphenol was also demonstrated as a suitable substrate, affording the corresponding sulfonylated product **3q** in 80% yield; meanwhile, with a higher temperature and an excessive amount of sulfonylation reagent, the 2,6-dimethylphenol could also be transformed into the corresponding product **3r** in 68% yield.

To further simplify the sulfonylation procedure, the transformation of hydroquinone **4** with sodium sulfinates was conducted in one step. By introducing PIDA as the oxidant and water as the solvent, the whole reaction proceeded immediately after charging all reagents in one flask together (conditions optimization see ESI†). As shown in Scheme 3, a variety of aryl and alkyl substituted sodium sulfinates were smoothly coupled with the hydroquinone and furnished the corresponding products in good to excellent yields (70–97%). It was noted that the best result of 97% yield was achieved when sodium 4-methylbenzenesulfinate **2a** was employed as the sulfonylation reagent.



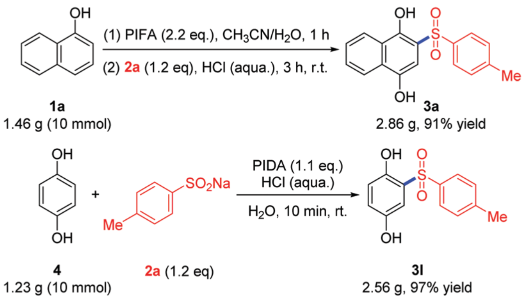
Scheme 3 Sulfonylation reactions with hydroquinone **4**[a,b]. [a]PIDA (0.33 mmol), hydroquinone **4** (0.30 mmol), H_2O (3.0 mL), aqueous HCl (0.30 mmol) and sodium sulfinate **2** (0.36 mmol) were added to a flask and stirred at room temperature for 5 min under air. [b] Isolated yields.



Scheme 4 Sulfonylation of 4-methoxyphenol in water.

Interestingly, on exposure of 4-methoxyphenol **5** to the mixture of PIDA, sulfonylnation reagent and aqueous HCl, the product **3l** was achieved in 61% yield (Scheme 4). According to the literature,[16] this result may be ascribed to the effect of solvent. Water was supposed to be involved in the oxidization process, the excessive amount of H_2O promoted the formation of *p*-quinone and was then followed by sulfonylation with sodium sulfinates to afford the product **3l**.

To further estimate the application possibility, the gram-scale synthesis studies were carried out. As shown in Scheme 5, both 1-naphthalenol **1a** and hydroquinone **4** were transformed



Scheme 5 Gram-scale synthesis.

into the corresponding products successfully with excellent yields under the optimized conditions, respectively. Significantly, the products could be easily isolated through a simple work-up process of filtration, washing with water and hexane.

Conclusions

To sum up, we have developed a one-pot method towards various sulfonylated hydroquinones and naphthalenediols in an aqueous medium with up to 97% yield. This metal-free transformation occurred smoothly with hypervalent iodine compounds as the oxidant. Both naphthols and phenols were viable with inexpensive and readily available sodium sulfinates as the sulfonylation reagents under an ambient atmosphere. This procedure is scalable, low-cost, experimentally simple, and the products could be easily obtained without column chromatography isolation. Further investigations of the synthesis and utility of these sulfonylated compounds are underway in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Natural Science Foundation of China (21702026 and 21861040) and Fundamental Research Funds for the Central Universities (N2005004 and N180705004) is acknowledged.

Notes and references

1 (*a*) E. Elhalem, B. N. Bailey, R. Docampo, I. Ujváry, S. H. Szajnman and J. B. Rodriguez, *J. Med. Chem.*, 2002, **45**, 3984–3999; (*b*) J. Wang, J. N. Park, X. Y. Wei and C. W. Lee, *Chem. Commun.*, 2003, 628–629; (*c*) K. Miyashita and T. Imanishi, *Chem. Rev.*, 2005, **105**, 4515–4536; (*d*) D. Nematollahi, S. Momeni and S. Khazalpour, *Electrochim. Acta*, 2014, **147**, 310–318; (*e*) J. Du, L. Ma, D. Shan, Y. Fan, L. Zhang, L. Wang and X. Lu, *J. Electroanal. Chem.*, 2014, **722–723**, 38–45; (*f*) A. Kamimura, T. Nokubi, R. Watanabe, M. Ishikawa, K. Nasu, H. Uno and M. Sumimoto, *J. Org. Chem.*, 2014, **79**, 1068–1083; (*g*) X. Li, Z. Zheng, H. Liu and Y. Gao, *Electrophoresis*, 2020, **41**, 1991–1999.

2 (*a*) J. T. Tsay, W. Oh, T. J. Larson, S. Jackowski and C. O. Rock, *J. Biol. Chem.*, 1992, **267**, 6807–6814; (*b*) M. M. Alhamadsheh, N. C. Waters, D. P. Huddler, M. Kreishman-Deitrick, G. Florova and K. A. Reynolds, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 879–883; (*c*) P. J. Lee, J. B. Bhonsle, H. W. Gaona, D. P. Huddler, T. N. Heady, M. Kreishman-Deitrick, A. Bhattacharjee, W. F. McCalmont, L. Gerena, M. Lopez-Sanchez, N. E. Roncal, T. H. Hudson, J. D. Johnson, S. T. Prigge and N. C. Waters, *J. Med. Chem.*, 2009, **52**, 952–963.

3 M. M. Alhamadsheh, N. C. Waters, S. Sachdeva, P. Lee and K. A. Reynolds, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6402–6405.

4 J. Vorkapić-Furac, T. Kishi, H. Kishi, T. H. Porter and K. Folkers, *Acta Pharm. Suec.*, 1977, **14**, 197–204.

5 R. C. Bernotas, R. R. Singhaus, D. H. Kaufman, J. M. Travins, J. W. Ullrich, R. Unwalla, E. Quinet, M. Evans, P. Nambi, A. Olland, B. Kauppi, A. Wilhelmsson, A. Goos-Nilsson and J. Wrobel, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 209–212.

6 (*a*) R. N. Warrener, D. A. C. Evans and R. A. Russell, *Tetrahedron Lett.*, 1984, **25**, 4833–4836; (*b*) D. E. Allgeier, S. A. Herbert, R. Nee, K. D. Schlecht and K. T. Finley, *J. Org. Chem.*, 2003, **68**, 4988–4990; (*c*) D. Habibi, A. Rahimi, A. Rostami and S. Moradi, *Tetrahedron Lett.*, 2017, **58**, 289–293; (*d*) S. Rouhani, A. Rostami, A. Salimi and O. Pourshiani, *Biochem. Eng. J.*, 2018, **133**, 1–11; (*e*) S. M. Maddox, G. A. Dawson, N. C. Rochester, A. B. Ayonon, C. E. Moore, A. L. Rheingold and J. L. Gustafson, *ACS Catal.*, 2018, **8**, 5443–5447.

7 (*a*) J. F. Bereznak and M. M. Joullié, *Synth. Commun.*, 1989, **19**, 3573–3578; (*b*) M. V. R. Reddy, S. Vijayalakshmi, D. B. Reddy and P. V. R. Reddy, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1991, **60**, 209–214; (*c*) Y. St-Denis, S. Lévesque, B. Bachand, J. J. Edmunds, L. Leblond, P. Préville, M. Tarazi, P. D. Winocour and M. A. Siddiqui, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1181–1184; (*d*) P. Lassalas, B. Gay, C. Lasfargeas, M. J. James, V. Tran, K. G. Vijayendran, K. R. Brunden, M. C. Kozlowski, C. J. Thomas, A. B. Smith, 3rd, D. M. Huryn and C. Ballatore, *J. Med. Chem.*, 2016, **59**, 3183–3203.

8 J. Yadav, B. Reddy, T. Swamy and N. Ramireddy, *Synthesis*, 2004, 1849–1853.

9 J. M. Bruce and P. Lloyd-Williams, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2877–2884.

10 B. Li, Y. Li, L. Yu, X. Wu and W. Wei, *Tetrahedron*, 2017, **73**, 2760–2765.

11 P.-G. Li, Y.-C. Li, T. Zhu, L.-H. Zou and Z. Wu, *Eur. J. Org. Chem.*, 2017, 6081–6084.

12 (*a*) B. Ge, D. Wang, W. Dong, P. Ma, Y. Li and Y. Ding, *Tetrahedron Lett.*, 2014, **55**, 5443–5446; (*b*) D. Wang, X. Yu, B. Ge, H. Miao and Y. Ding, *Chin. J. Org. Chem.*, 2015, **35**, 676–680; (*c*) X. Yu, Q. Wu, H. Wan, Z. Xu, X. Xu and D. Wang, *RSC Adv.*, 2016, **6**, 62298–62301; (*d*) L. Wang, Y.-B. Xie, Q.-L. Yang, M.-G. Liu, K.-B. Zheng, Y.-L. Hu and N.-Y. Huang, *J. Iran. Chem. Soc.*, 2016, **13**, 1797–1803.

13 (*a*) Y. Tamura, T. Yakura, J. Haruta and Y. Kita, *J. Org. Chem.*, 1987, **52**, 3927–3930; (*b*) Y. Tamura, T. Yakura, H. Tohma, K. Kikuchi and Y. Kita, *Synthesis*, 1989, 126; (*c*) Y. Kita, T. Dohi, T. Nakae, N. Takenaga, T. Uchiyama, K.-I. Fukushima and H. Fujioka, *Synthesis*, 2012, 1183–1189.

14 (*a*) Y. Kita, T. Yakura, H. Tohma, K. Kikuchi and Y. Tamura, *Tetrahedron Lett.*, 1989, **30**, 1119–1120; (*b*) S. Sarkar, M. K. Ghosh and M. Kalek, *Tetrahedron Lett.*, 2020, **61**, 152459.

15 (*a*) Y. Ogata, Y. Sawaki and M. Isono, *Tetrahedron*, 1969, **25**, 2715–2721; (*b*) M. P. Lockshin, M. P. Filosa and M. J. Zuraw, *J. Org. Chem.*, 1996, **61**, 2556–2558; (*c*) D. E. Allgeier,

S. A. Herbert, R. N. Kenneth, D. Schlecht and K. T. Finley, *J. Org. Chem.*, 2003, **68**, 4988–4990.

16 (*a*) R. Barret and M. Daudon, *Tetrahedron Lett.*, 1990, **31**, 4871–4872; (*b*) R. M. Moriarty and O. Prakash, in *Organic Reactions*, ed. L. E. Overman, *et al.*, John Wileys & Sons, Inc, Hoboken, 2001, ch. 2, pp. 327–333; (*c*) A. Wu, Y. Duan, D. Xu, T. M. Penning and R. G. Harvey, *Tetrahedron*, 2010, **66**, 2111–2118; (*d*) L. Pouységu, D. Deffieux and S. Quideau, *Tetrahedron*, 2010, **66**, 2235–2261; (*e*) K. Signo, Z. Mammasse and S. Canesi, *J. Org. Chem.*, 2020, **85**, 2832–2837.