Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Z. Chen, L. Tong, Z. Du, Z. Mao, X. Zhang, Y. Zou and M. Yan, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB00293B.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB00293B

Journal Name

COMMUNICATION

Annulation of β-naphthols and 1,4-hydroxycoumarins with vinylsulfonium salts: Synthesis of dihydrofuran derivatives

Zi-cong Chen,[a] Lang Tong,[a] Zhi-bo Du,[b] Zhi-feng Mao,*[a] Xue-jing Zhang,[a] Yong Zou[a] and Ming Yan*[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A new synthetic approach to dihydrofuran derivatives via the annulation reaction of β-naphthols and 4-hydroxycoumarins with vinylsulfonium salts had been developed. A variety of dihydrofuran derivatives were prepared in moderate to good yields under mild conditions. The products could be readily transformed to the corresponding furans via the dehydrogenation with DDQ.

Furans and dihydrofurans are important structural units widely found in natural products and synthetic drugs (Fig. 1).[1] For example, ramelteon is a highly selective MT1/MT2 melatonin receptor agonist for the treatment of insomnia.[1e] Psoralen isolated from *fructus psoraleae* possesses promising anticancer activity.[1f] Glabramycin C and reductiomycin are antibiotics with potent antibacterial activity.[1g, 1h] In the past decades, the synthesis of furans and dihydrofurans has received great attentions and a variety of methods had been developed.[2] Despite the progresses, new synthetic approaches are still desirable considering the structural diversities of furan and dihydrofuran derivatives.[3]

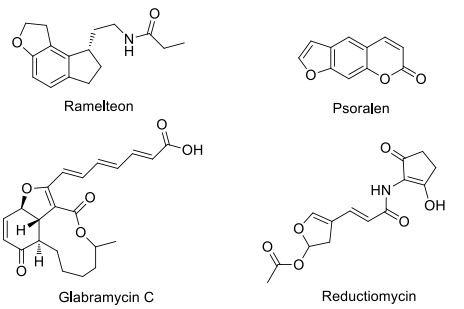


Figure 1 Representative natural products and synthetic drugs containing furan or dihydrofuran moiety.

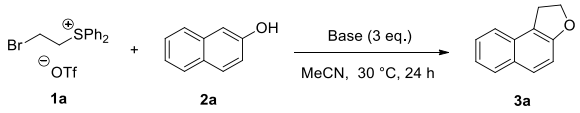
Vinylsulfonium salts are a class of good Michael acceptors which undergo the cascade addition/cyclization with a variety of nucleophiles.[4] Their reactions with active methylene compounds provided cyclopropanes.[5] Vinylsulfonium salts are also valuable for the synthesis of nitrogen heterocycles via the reactions with amines or amides.[6] The synthesis of furans or dihydrofurans from vinylsulfonium salts were also developed.[7] Stirling and co-workers reported that furans could be obtained via the addition of enolate anions to allenic sulfonium salts.[7a-7c] Ojida and co-workers found that the reactions of 1,3-dicarbonyl compounds with prop-2-ynylsulfonium salts provided furans and dihydrofurans.[7d-7f] The synthesis of epoxide-fused or cyclopropane-fused tetrahydrofurans was also achieved by Aggarwal and co-workers using α-hydroxy aldehydes/ketones as the substrates.[6i,7g-7h] In the reaction of 1,3-dicarbonyl compounds with β-(trifluoromethyl)vinyl sulfonium salt, trifluoromethyl substituted dihydrofurans were obtained with good yields while NaH was used as base in THF/CH_2Cl_2 at -78 °C. Interestingly, the same reaction provided trifluoromethyl substituted cyclopropanes as the major products in DMSO at room temperature.[5f] However, the potentials of vinylsulfonium salts for the synthesis of furan and dihydrofuran derivatives remain to be explored. In this paper, we report an efficient synthesis of dihydrofuran and furan derivatives via the cascade reaction of vinylsulfonium salts with β-naphthols and 4-hydroxycoumarins.

We commenced our study with the reaction of (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate **1a** with β-naphthol **2a**. **1a** was used as a precursor of vinylsulfonium salt in the presence of bases.[6d,11] 1,2-Dihydronaphtho[2,1-*b*]-furan **3a** was previously prepared via the reaction of *in situ* generated *O*-quinone methides with dimethyl sulfoxonium methylide.[8] A range of bases were tested and the results are summarized in Table 1. Pyridine, triethylamine, DIPEA, and DABCO did not provide the product **3a** (Table 1, entries 1-4). To our delight, **3a** was obtained in a low yield while using DBU as the base (Table 1, entry 5). On the other hand, inorganic bases were found to be more effective

[a] *Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China.*
E-mail: zhifengmao01@163.com; yanming@mail.sysu.edu.cn
[b] *Zhongshan WanHan Pharmaceutical Co., Ltd, Zhongshan 528451, China.*
†Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, and copies of ^1H, ^{19}F and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

(Table 1, entries 6-9). Moderate yields were obtained with K_3PO_4 and Cs_2CO_3. A good yield was achieved with K_2CO_3 (Table 1, entry 8). Stronger bases such as KOH and NaH led to reduced yields (Table 1, entries 9-10). Furthermore, the effect of the reaction solvent was examined (Table 1, entries 11-19). Moderate yields were obtained in toluene and dichloromethane (DCM). Poor yields were observed in THF and 1,4-dioxane. The reaction in acetone, DMF and DMSO provided **3a** in moderated yields. Protonic solvent such as MeOH was incompatible with the reaction. MeCN was identified as the best solvent. Increasing the equivalent of **1a** provided slightly higher yields (Table 1, entries 19-20). The excellent yield was achieved at 0 °C, but the further decrease of the reaction temperature led to the significant loss of the yield (Table 1, entries 21-22).

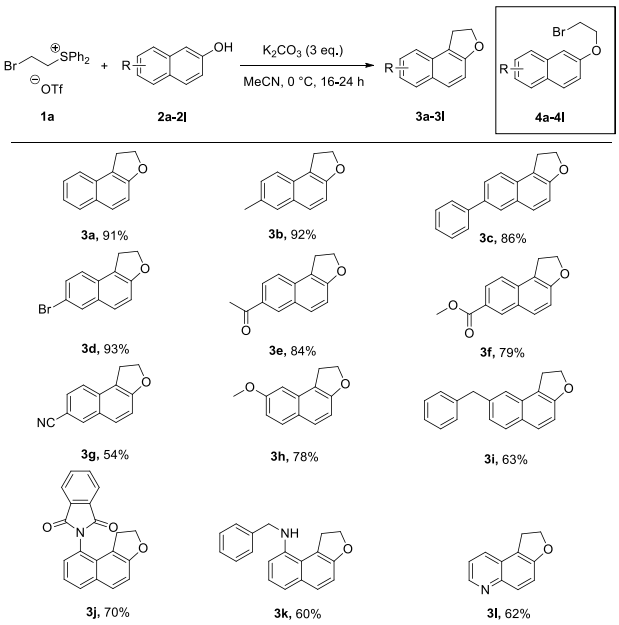
Table 1 Optimization of reaction conditions[a]



Entry	Base	1a/2a/base	Solvent	Yield (%)[b]
1	pyridine	1:1:3	MeCN	-
2	Et_3N	1:1:3	MeCN	-
3	DIEA	1:1:3	MeCN	-
4	DABCO	1:1:3	MeCN	-
5	DBU	1:1:3	MeCN	41
6	K_3PO_4	1:1:3	MeCN	62
7	Cs_2CO_3	1:1:3	MeCN	67
8	K_2CO_3	1:1:3	MeCN	83
9	KOH	1:1:3	MeCN	47
10	NaH	1:1:3	MeCN	34
11	K_2CO_3	1:1:3	toluene	50
12	K_2CO_3	1:1:3	DCM	50
13	K_2CO_3	1:1:3	THF	36
14	K_2CO_3	1:1:3	1,4-dioxane	24
15	K_2CO_3	1:1:3	acetone	65
16	K_2CO_3	1:1:3	DMF	68
17	K_2CO_3	1:1:3	DMSO	54
18	K_2CO_3	1:1:3	MeOH	0
19	K_2CO_3	1.2:1:3	MeCN	84
20	K_2CO_3	1.5:1:3	MeCN	87
21[c]	K_2CO_3	1.5:1:3	MeCN	96
22[d]	K_2CO_3	1.5:1:3	MeCN	36

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.2 mmol), **2a** (0.2 mmol), base (0.6 mmol), and solvent (4.0 mL) at room temperature under an argon atmosphere for 24 h. [b] GC Yields with dodecane as the internal standard. [c] The reaction was carried out at 0 °C. [d] The reaction was carried out at -20 °C.

Table 2 Reaction of **1a** with β-naphthols **2a-2k** and quinolin-6-ol[a,b]



[a] Reaction conditions: **1a** (0.3 mmol), **2a-2l** (0.2 mmol), K_2CO_3 (0.6 mmol), MeCN (4 mL), 0 °C, 16-24 h, under an argon atmosphere. [b] Isolated yields.

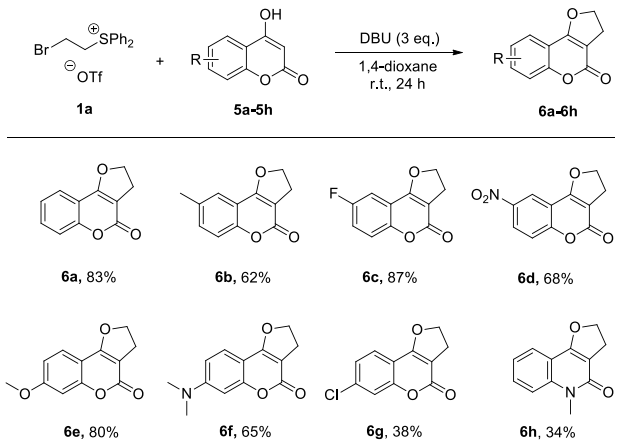
With the optimized conditions, we investigated the reaction of **1a** with a range of β-naphthols **2a**-**2k** and the results are summarized in Table 2. 6-Substitution of β-naphthol with Me, Ph and Br was tolerated very well and the products **3b**-**3d** were obtained in excellent yields. However, 6-substitution with electron-withdrawing groups (MeCO, CO_2Me, and CN) led to reduced yields (**3e**-**3g**). 7-MeO and 7-Bn substituted β-naphthols gave **3h**-**3i** in moderate yields. β-Naphthols with 8-*N*-phthaloylimino and 8-benzylamino were also applicable. The products **3j**-**3k** were obtained in moderate yields. In the case of substrate **2k**, no side product from the nucleophilic attack of the amino group was observed. We speculated that the big steric hindrance of the amine group prevented its reaction with **1a**. In addition, the structurally similar quinolin-6-ol **2l** was examined. The product **3l** was obtained in a moderate yield. During the reactions, we observed small amount of *O*-β-bromoethyl byproducts **4a**-**4l** in combination with **3a**-**3l** via ^{1}H NMR analysis. In a previous study, Minami and co-workers reported that the phenoxy anion can substitute dimethyl sulfide from 3-methylbutenyl dimethylsulfonium salts.[9] **4a**-**4l** were probably generated through the direct substitution of diphenyl sulfide by the β-naphthoxy anions. **4a**-**4l** are difficult to be separated from **3a**-**3l** by column chromatography. After testing a series of conditions, we found that **4a**-**4l** could be removed via the addition of piperazine before the work-up.[10]

Furthermore, the reaction of **1a** with 4-hydroxycoumarins **5a**-**5h** was examined and the results are summarized in Table 3. K_2CO_3/MeCN system is not optimal for the transformation. After the screening of reaction conditions, DBU/1,4-dioxane system was found to be more efficient.[10] The reaction of 4-hydroxycoumarin **5a** gave the expected dihydrofuran **6a** in a good yield. 4-Hydroxycoumarins with 6-Me, 6-F, and 6-NO_2

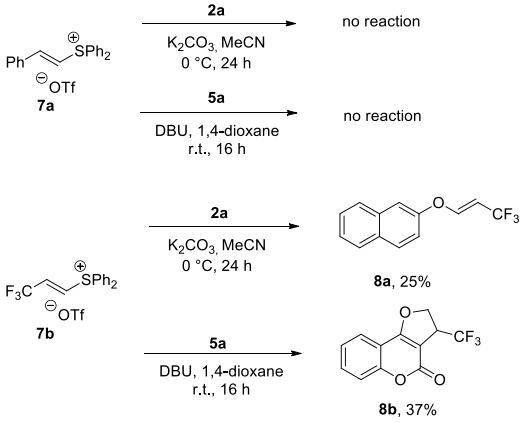
DOI: 10.1039/C8OB00307B

substitutions gave the products **6b**-**6d** in moderate to good yields. 7-Substitutions with methoxyl and dimethylamino were tolerated well. The products **6e** and **6f** were obtained in good yields. However, 7-chloro substitution led to a poor yield (**6g**). 4-Hydroxy-1-methyl-2-quinolone (**5h**) was also examined and the corresponding product **6h** was obtained in a low yield.

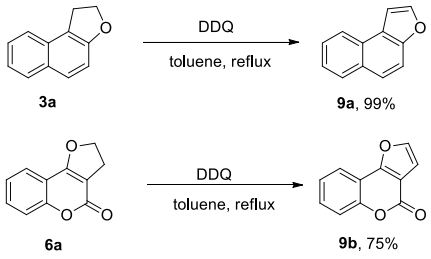
Table 3 Reactions of **1a** with 4-hydroxycoumarins **5a**-**5g** and 4-hydroxy-1-methyl-2-quinolone **5h**[a,b]



[a] Reaction conditions: **1a** (0.3 mmol), **5a**-**5h** (0.2 mmol), DBU (0.6 mmol), 1,4-dioxane (4 mL), r.t., 24 h, under an argon atmosphere. [b] Isolated yields.



Scheme 1 Reactions of **7a**, **7b** with β-naphthol **2a** and 4-hydroxycoumarin **5a**.

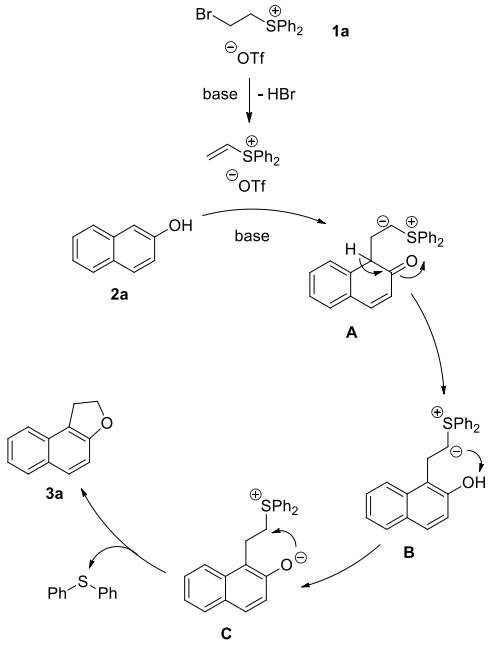


Scheme 2 Synthesis of furans **9a** and **9b.**

β-Phenyl vinylsulfonium salt **7a** and β-trifluoromethyl vinylsulfonium salt **7b** were also prepared. Their reactions with β-naphthol **2a** and 4-hydroxycoumarin **5a** were examined and the results are showed in Scheme 1. The β-substitution of vinylsulfonium salts decreased the reactivity significantly. β-Phenyl vinylsulfonium salt **7a** is unreactive with **2a** or **5a**. The reaction of β-trifluoromethyl vinylsulfonium salt **7b** with β-naphthol **2a** did not give the expected dihydrofuran derivative. Instead, small amount of enol ether **8a** was obtained. The reaction of **7b** with 4-hydroxycoumarin **5a** provided the dihydrofuran **8b**, however, in a low yield.

Dihydrofurans **3a** and **6a** were transformed to the corresponding furans **9a** and **9b** in good yields via the dehydrogenation with DDQ (Scheme 2). The result demonstrated the potential of this method for the synthesis of both dihydrofurans and furans.

A tentative reaction mechanism is outlined in scheme 3. The reaction begins with the generation of vinylsulfonium salt via the elimination of hydrogen bromide from **1a**.[12] The vinylsulfonuim salt reacts with β-naphthol **2a** to give sulfonium ylide **A**, which then tautomerizes to intermediate **B**. After a proton transfer, the zwitterion **C** is formed. The subsequent intramolecular SN_2 reaction yields the product **3a** and eliminates diphenyl sulfide.



Scheme 3 Proposed reaction mechanism.

Conclusions

We have developed a new approach to prepare dihydrofuran derivatives via the cascade reaction of β-naphthols and 4-hydroxycoumarins with vinylsulfonium salts. A series of dihydrofurans were obtained in moderate to good yields. The products could be converted to the corresponding furans in good yields after the dehydrogenation with DDQ. The reaction

procedure is simple and the substrates are readily available. This method is practical for the synthesis of a variety of dihydrofurans and furans. The application of this approach for the synthesis and the screen of biologically active furan derivatives are currently underway.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 21772240, 21472248), Guangzhou Science Technology and Innovation Commission (201707010210), Department of Science and Technology of Guangdong Province (2017A020211011), and National Science and Technology Major Project of the Ministry of Science and Technology of China (2017ZX09305010) for the financial support of this study.

Notes and references

1 For the examples of natural products and synthetic drugs containing furan or dihydrofuran moiety, see: (a) M. M. Bandurraga, W. Fenical, S. F. Donovan and J. Clardy, *J. Am. Chem. Soc.*, 1982, **104**, 6463; (b) A. T. Merrit and S. V. Ley, *Nat. Prod. Rep.*, 1992, **9**, 243; (c) M. Cases, F. Gonzalez-Lopez de Turiso, M. S. Hadjisoteriou and G. Pattenden, *Org. Biomol. Chem.*, 2005, **3**, 2786; (d) A. Roy and S. Saraf, Biol. *Pharm. Bull.*, 2006, **29**, 191; (e) A. Kuriyama, M. Honda and Y. Hayashino, *Sleep Medicine*, 2014, **15**, 385; (f) G. D. Cimino, H. B. Gamper, S. T. Isaacs and J. E. Hearst, *Annu. Rev. Biochem.*, 1985, **54**, 1151; (g) H. Jayasuriya, D. Zink, A. Basilio, F. Vicente, J. Collado, G. Bills, M. L. Goldman, M. Motyl, J. Huber, G. Dezeny, K. Byrne and S. B. Singh, *J. Antibiotics*, 2009, **62**, 265; (h) H. Cho, J. M. Beale, C. Graff, U. Mocek, A. Nakagawa, S. Omura and H. G. Floss. *J. Am. Chem. Soc.*, 1993, **115**, 12296.

2 For the reviews of the synthesis of furans, see: (a) H. Kwiecien, M. Smist and M. Kowalewska, *Curr. Org. Synth.*, 2012, **9**, 529; (b) K. S. Yeung, X. S. Peng, J. Wu, R. H. Fan, X. L. Hou, *Pro. Heterocycl. Chem.*, 2013, **25**, 183; (c) J. V. Ruppel, N. L. Snyder, A. D. Thompson, T. W. Farnsworth, in *Heterocyclic Chemistry in Drug Discovery*, edited by J. J. Li, John Wiley & Sons, New Jersey, 2013; (d) W. J. Moran and A. Rodríguez, *Org. Prep. Proced. Int.*, 2012, **44**, 103.

3 For the recent reports of furan synthesis, see: (a) A. O. Chagarovsky, E. M. Budynina, O. A. Ivanova, E. V. Villemson, V. B. Rybakov, I. V. Trushkov and M. Y. Melnikov, *Org. Lett.*, 2014, **16**, 2830; (b) F. L. Zhu, Y. H. Wang, D. Y. Zhang, J. Xu and X. P. Hu, *Angew. Chem., Int. Ed.*, 2014, **53**, 10223; (c) T. Nakano, K. Miyazaki and A. Kamimura, *J. Org. Chem.*, 2014, **79**, 8103; (d) T. Naveen, R. Kancherla and D. Maiti, *Org. Lett.*, 2014, **16**, 5446; (e) M. Ghosh, S. Mishra, K. Monir and A. Hajra, *Org. Biomol. Chem.*, 2015, **13**, 309; (f) S. Tang, K. Liu, Y. Long, X. T. Qi, Y. Lan and A. W. Lei, *Chem. Commun.*, 2015, **51**, 8769; (g) C. Xue, X. Huang, S. Z. Wu, C. L. Fu and S. M. Ma, *Org. Chem. Front.*, 2016, **3**, 588; (h) D. Y. Li, H. J. Chen and P. N. Liu, *Angew. Chem., Int. Ed.*, 2016, **55**, 373; (i) Y. S. Zhao, S. Q. Li, X. S. Zheng, J. B. Tang, Z. J. She, G. Gao and J. S. You, *Angew. Chem., Int. Ed.*, 2017, **56**, 4286.

4 (a) Z. Wang and L. S. Jimenez, *J. Am. Chem. Soc.*, 1994, **116**, 4977; (b) Y. F. Wang, W. H. Zhang, V. J. Colandrea and L. S. Jimenez, *Tetrahedron*, 1999, **55**, 10659; (c) M. G. Unthank, N. Hussain and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2006, **45**, 7066; (d) S. Catalán-Muñoz, C. A. Müller and S. V. Ley, *Eur. J. Org. Chem.*, 2010, 183.

5 (a) J. Gosselck and G. Schmidt, *Tetrahedron Lett.*, 1969, **31**, 2615; (b) K. Takaki, H. Takahashi, Y. Ohshiro and T. Agawa, *J. Chem. Soc., Chem. Commun.*, 1977, 675; (c) K. Takaki and T. Agawa, *J. Org. Chem.*, 1977, **42**, 3303; (d) K. Takaki, K. Negoro and T. Agawa, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1490; (e) Y. L. Chow, B. H. Bakker and K. Iwai, *J. Chem. Soc., Chem. Commun.*, 1980, 521; (f) H. Lin, Q. L. Shen. and L. Lu, *J. Org. Chem.*, 2011, **76**, 7359; (g) P. Gopinath and S. Chandrasekaran, *J. Org. Chem.*, 2011, **76**, 700; (h) Z. J. Mao, H. J. Qu, Y. Y. Zhao and X. F. Lin, *Chem. Commun.*, 2012, **48**, 9927; (i) N. Kasai, R. Maeda, H. Furuno and T. Hanamoto, *Synthesis*, 2012, **44**, 3489; (j) K. Hirotaki, Y. Takehiro, R. Kamaishi, Y. Yamada and T. Hanamoto, *Chem. Commun.*, 2013, **49**, 7965; (k) T. Ishikawa, N. Kasai, Y. Yamada and T. Hanamoto, *Tetrahedron*, 2015, **71**, 1254; (l) M. W. Zhou, K. En, Y. M. Hu, Y. F. Xu, H. C. Shen and X. H. Qian, *RSC Adv.*, 2017, **7**, 3741.

6 For the selected examples, see: (a) J. Matsuo, H. Yamanaka, A. Kawana and T. Mukaiyama, *Chem. Lett.*, 2003, **32**, 392; (b) M. Yar, E. M. McGarrigle and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2008, **47**, 3784; (c) M. G. Unthank, B. Tavassoli and V. K. Aggarwal, *Org. Lett.*, 2008, **10**, 1501; (d) M. Yar, E. M. McGarrigle and V. K. Aggarwal, *Org. Lett.*, 2009, **11**, 257; (e) R. Maeda, K. Ooyama, R. Anno, M. Shiosaki, T. Azema and T. Hanamoto, *Org. Lett.*, 2010, **12**, 2548; (f) C. S. Xie, D. Y. Han, Y. Hu, J. H. Liu, T. Xie, *Tetrahedron Lett.*, 2010, **51**, 5238; (g) E. M. McGarrigle, S. P. Fritz, L. Favereau, M. Yar and V. K. Aggarwal, *Org. Lett.*, 2011, **13**, 3060; (h) J. An, N. J. Chang, L. D. Song, Y. Q. Jin, Y. Ma, J. R. Chen and W. J. Xiao, *Chem. Commun.*, 2011, **47**, 1869; (i) S. P. Fritz, J. V. Matlock, E. M. McGarrigle and V. K. Aggarwal, *Chem. Eur. J.*, 2013, **19**, 10827; (j) J. V. Matlock, S. P. Fritz, S. A. Harrison, D. M. Coe, E. M. McGarrigle and V. K. Aggarwal, *J. Org. Chem.*, 2014, **79**, 10226; (k) J. V. Matlock, T. D. Svejstrup, P. Songara, S. Overington, E. M. McGarrigle and V. K. Aggarwal, *Org. Lett.*, 2015, **17**, 5044; (l) P. H. Jia, Q. L. Zhang, Q. M. Ou and Y. Huang, *Org. Lett.*, 2017, **19**, 4664; (m) P. H. Jia, Q. L. Zhang, H. X. Jin and Y. Huang, *Org. Lett.*, 2017, **19**, 412.

7 (a) J. W. Batty, P. D. Howes and C. J. M. Stirling, *Chem. Commun.*, 1971, 534; (b) J. W. Batty, P. D. Howes and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 1*, 1973, 65; (c) P. D. Howes and C. J. M. Stirling, *Org. Synth.,* 1973, **53**, 1; (d) M. Aso, M. Sakamoto, N. Urakawa and K. Kanemastsu, *Heterocycles*, 1990, **31**, 1003; (e) M. Aso, A. Ojida, G. Yang, O. J. Cha and E. Osawa, *J. Org. Chem.*, 1993, **58**, 3960; (f) A. Ojida, F. Tanoue and K. Kanematsu, *J. Org. Chem.*, 1994, **59**, 5970; (g) S. P. Fritza, Z. Alia, M. G. Unthank, E. M. McGarrigle and V. K. Aggarwal, *Helv. Chim. Acta.*, 2012, **95**, 2384; (h) S. P. Fritz, T. H. West, E. M. McGarrigle and V. K. Aggarwal, *Org. Lett.*, 2012, **14**, 6370.

8 (a) E. Breuer and D. Melumad, *Tetrahedron Lett.*, 1969, **23**, 1875; (b) A. Blade´-Font and T. de Mas Rocabayera, *J. Chem. Soc., Perkin Trans. 1*, 1982, 841.

9 T. Minami, I. Niki, and T. Agawa, *Phosphorus and Sulfur and the Related Elements*, 1977, **3**, 55.

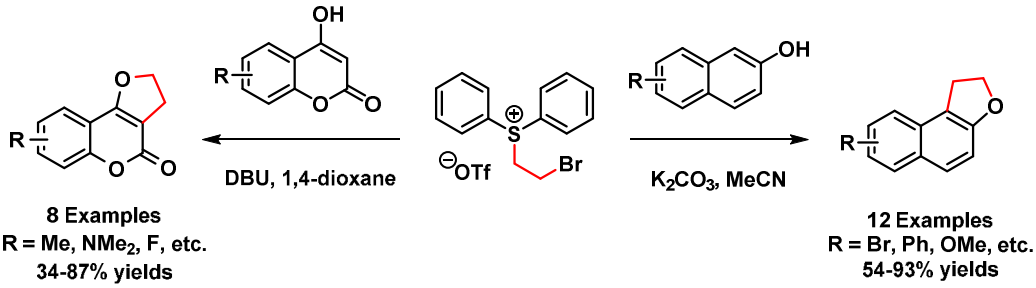
10 see supporting information for the details.

11 V. G. Nenajdenko, P. V. Vertelezkij, I. D. Gridnev, N. E. Shevchenko and E. S. Balenkova, *Tetrahedron*, 1997, **53**, 8173.

12 The generation of vinyl sulfonium salt was confirmed via the ^{1}H NMR analysis of the reaction mixture in d^6-DMSO. In addition, the vinyl sulfonium salt was also prepared according to the reported procedure (ref. 6b) and was used in the reaction with β-naphthol **2a**. The product **3a** was obtained with a similar yield (90%).

View Article Online
DOI: 10.1039/C8OB00293B

Contents entry



Annulation reaction of vinylsulfonium salt with β-naphthols and 4-hydroxycoumarins provided dihydrofuran derivatives in moderate to good yields under mild conditions.