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Triflic acid promoted solvent free synthesis of densely functionalized furans†

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A simple, efficient and novel methodology has been developed for the synthesis of densely substituted furans mediated by triflic acid. The current protocol proceeds in a domino fashion, the initial step involves Friedel–Crafts arylation, followed by dehydrative cyclization. It is operationally simple and can be carried out under solvent free conditions.

Introduction

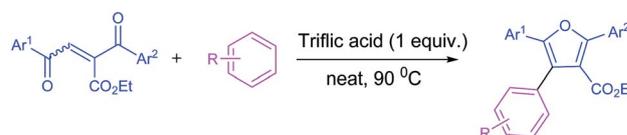
Furan and its derivatives constitute a significant class of heterocyclic compounds, they act as key structural units in various natural products, bioactive compounds and agrochemicals.¹ They serve as important building blocks in the construction of complex natural molecules.² Recently the synthesis of densely functionalized furans attained much attention in modern organic chemistry due to their wide range of applications in medicinal chemistry and material sciences.³ Compounds containing the furan moiety were found to demonstrate diverse biological activities such as anticancer,⁴ antifungal,⁵ antimicrobial,⁶ antibacterial,⁷ and antispasmodic activity.⁸ Apart from these, furan derivatives also exhibit herbicidal activity.⁹ Several synthetic strategies have been developed for the synthesis of multi-substituted furans such as functionalization of furans,¹⁰ metal catalyzed,¹¹ 3 + 2 annulations,¹² and intramolecular cyclization reactions.¹³ Though all these methods were found to be efficient in synthesizing the substituted furan derivatives they suffer from a few drawbacks such as use of expensive metal catalysts, solvents and employing harsh reaction conditions. Therefore, it is enviable to develop simple, cost effective and environment friendly protocols for the synthesis of densely functionalized furan derivatives from the easily accessible starting materials. Herein, we report a novel and versatile strategy for the synthesis of furan derivatives mediated by triflic acid under solvent free conditions.

Results and discussion

In our preliminary experiment we have carried out the reaction of **1a** with 1,3-dimethoxybenzene (**2a**) in presence of molecular

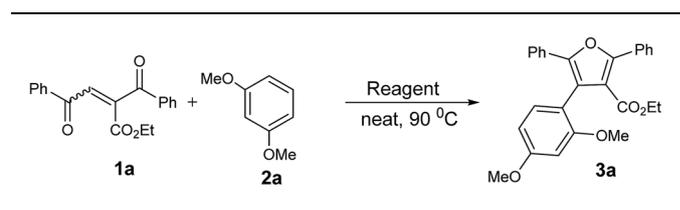
iodine, at 90 °C, the reaction underwent smoothly and afforded the desired furan derivative ethyl 4-(2,4-dimethoxyphenyl)-2,5-diphenylfuran-3-carboxylate (**3a**) in 55% yield (Scheme 1).

The product thus obtained was confirmed by the analysis ¹H and ¹³C NMR spectral data. The result obtained was encouraging and we focused on optimizing the reaction conditions in presence of various Bronsted acids. Accordingly when the reaction was carried out in presence of *p*-toluenesulfonic acid monohydrate (*p*-TSA·H₂O) and methanesulphonic acid, we were pleased to isolate the product **3a** in 82 and 86% yields



Scheme 1 Triflic acid mediated synthesis of furan derivatives.

Table 1 Optimization of reaction conditions^a



Entry	Reagent	Time (h)	Yield ^b (%)
1	I ₂	5	55
2	<i>p</i> -TSA·H ₂ O	4	82
3	CH ₃ SO ₃ H	4	86
4	TFA	4	84
5	TfOH	2	94

^a All reactions were performed with **1a** (1 mmol), 1,3-dimethoxybenzene (**2a**) (1.5 mmol), reagent (1 mmol) under neat conditions. ^b Yields of pure and isolated products.

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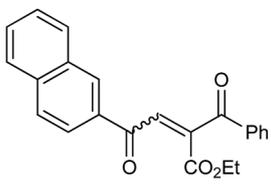
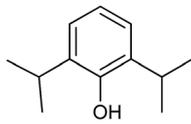
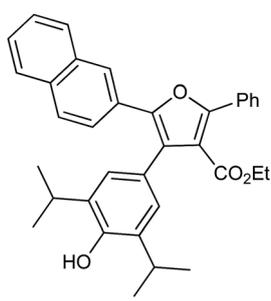
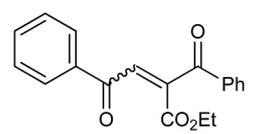
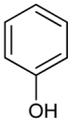
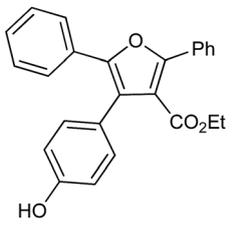
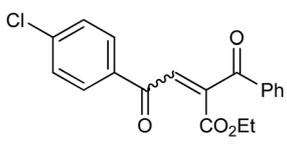
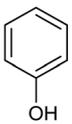
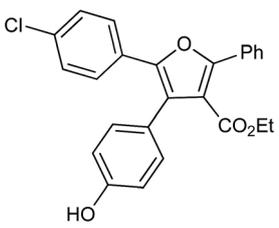


Table 2 Scope of substrate^{a,b}

Entry	1,4-Dienone	Benzene derivatives	Product	Yield ^b (%)
	 1a-c	 2a-c	 3a-h	
	Triflic acid (1 equiv.) neat, 90 °C, 2h			
1			 3a	94
2			 3b	88
3			 3c	92
4			 3d	84
5			 3e	87



Table 2 (Contd.)

Entry	1,4-Dienone	Phenol	Product	Yield ^b (%)
6				82
7				91
8				81

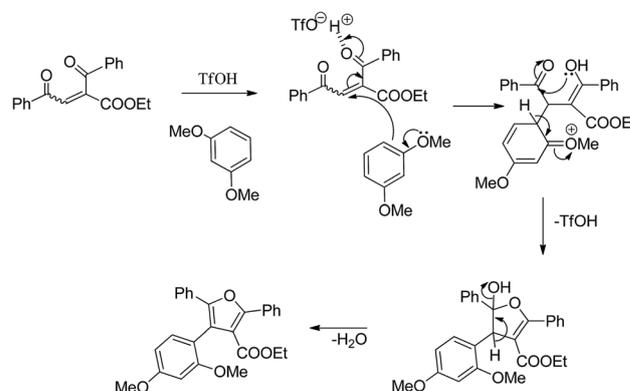
^a All reactions were performed with **1a-c** (1 mmol), benzene derivatives (1.5 mmol), TfOH (1 mmol) under neat conditions. ^b Yields of pure and isolated products.

respectively (Table 1, entry 2 & 3). The similar reaction promoted by trifluoroacetic acid (TFA) provided the product in 84% yield in 4 h (Table 1, entry 4). When we employed triflic acid (TfOH) as a reagent surprisingly, the reaction was completed in 2 h and the product **3a** was isolated in 94% yield (Table 1, entry 5).

With the optimized reaction conditions, we further proceeded to explore the scope of substrates in the current protocol. Therefore, the starting materials **1a**, **1b** and **1c** were synthesized following the literature procedure.¹⁴ Under the standard reaction condition, the compounds **1b** and **1c** were reacted with 1,3-dimethoxybenzene, the reaction proceeded well and after purification by column chromatography the corresponding furan derivatives **3b** and **3c** were obtained in 88 and 92% yields (Table 2, entries 2–3). When the reactivity of 2,6-diisopropylphenol was examined with the 1,4-dienones **1a**, **1b** and **1c**, we were pleased to observe that the reactions have undergone smoothly even in presence of bulky iso-propyl groups and gave the desired products in 84, 87 and 82% yields respectively (Table 2, entries 4–6). Furthermore, the reactions of **1a** and **1b** with phenol in presence of TfOH acid underwent effectively to deliver the desired products in 91 and 81% yields (Table 2, entries 7–8). Purity of all the products was confirmed by the analysis of IR, Mass, ¹H and ¹³C NMR spectral data.

Mechanism

In the initial step of the reaction of **1a** with 1,3-dimethoxybenzene in presence of triflic acid, the 1,3-dimethoxybenzene reacts with **1a** via Friedel–Crafts reaction to give 1,4-dione intermediate. Thus obtained 1,4-dione, further undergoes the acid-mediated intramolecular cyclization by elimination of water molecule to give the furan derivative **3a** (Scheme 2).



Scheme 2 Proposed mechanism for synthesis of furan and its derivatives.



Conclusion

In conclusion we have developed triflic acid mediated novel, efficient protocol for the synthesis of densely functionalized furan derivatives from the simple starting materials. The current strategy is easy to handle and provides an access to the synthesis of diversely substituted furan derivatives in excellent yields.

Experimental section

General information

Triflic acid, 1,4-dienone, 1,3-dimethoxy benzene and other starting materials were purchased from Sigma Aldrich and Fluka were used without purification. All experiments were carried out under air. Column chromatography was carried out with silica gel 60–120 sized mesh using hexane and ethyl acetate as eluents. Analytical TLC was performed with silica gel 60 F254 plates (Merck), and the products were visualized by UV detection. ¹H-NMR and ¹³C-NMR (Avance 300, Innova 400 MHz and Bruker Gemini 200 MHz) spectra were recorded in CDCl₃ using TMS as internal standard. Chemical shifts (δ) are reported in ppm, and spin–spin coupling constants (J) are in Hz. Melting points were determined on a Fisher-Johns melting point apparatus. FT-IR and MS were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrometer and Finnegan MAT 1020 mass spectrometer operating at 70 eV.

Representative experimental procedure for the synthesis of furan derivatives using triflic acid. To mixture of 1,4-dienone **1a** (1.0 mmol) and 1,3-dimethoxybenzene (**2a**) (1.5 mmol), TfOH (1.0 mmol) was added and the resulting reaction mixture was stirred at 90 °C for 2 h. After completion of reaction as shown by TLC, the reaction mixture was diluted with 10 mL of DCM. The organic layer was washed with saturated NaHCO₃ solution (10 mL), followed by water (2 × 10 mL). The organic layer was separated, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. Thus obtained crude reaction mixture was purified by silica gel column chromatography to afford the product **3a** Ethyl 4-(2,4-dimethoxyphenyl)-2,5-diphenylfuran-3-carboxylate in 94% yield.

Acknowledgements

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References

- (a) B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795; (b) M. Gutierrez, T. L. Capson, H. M. Guzman, J. Gonzalez, E. Ortega-Barria, E. Quinoa and R. Riguera, *J. Nat. Prod.*, 2005, **68**, 614; (c) M. C. Sanchez, M. J. Ortega, E. Zubia and J. L. Carballo, *J. Nat. Prod.*, 2006, **69**, 1749; (d) J. Marrero, J. Benitez, A. D. Rodriguez, H. Zhao and R. G. Raptis, *J. Nat. Prod.*, 2008, **71**, 381; (e) M. G. Missakian, B. J. Burresons and P. J. Scheuer, *Tetrahedron*, 1975, **31**, 2513; (f) R. Kazlauskas, P. T. Murphy, R. J. Wells, J. J. Daly and P. Schonholze, *Tetrahedron Lett.*, 1978, **49**, 4951; (g) M. V. R. Reddy, S. Lakshman, A. V. R. Rao, Y. Venkateswarlu and V. J. Rao, *J. Nat. Prod.*, 1993, **56**, 970; (h) J. Kobayashi, D. Watanabe, N. Kawasaki and M. Tsuda, *J. Org. Chem.*, 1997, **62**, 9236; (i) A. Rudi, T. L.-A. Dayan, M. Aknin, E. M. Gaydou and Y. Kashman, *J. Nat. Prod.*, 1998, **61**, 872; (j) Y.-L. Lin, Y.-L. Tsai, Y.-H. Kuo, Y.-H. Liu and M.-S. Shiao, *J. Nat. Prod.*, 1999, **62**, 1500.
- (a) T. Nagata, M. Nakagawa and A. Nishida, *J. Am. Chem. Soc.*, 2003, **125**, 7484; (b) S. F. Kirsch, *Org. Biomol. Chem.*, 2006, **4**, 2076; (c) P. A. Roethle and D. Trauner, *Org. Lett.*, 2006, **8**, 345; (d) T. Montagnon, M. Tofi and G. Vassilikogiannakis, *Acc. Chem. Res.*, 2008, **41**, 1001; (e) D. Kalaitzakis, M. Triantafyllakis, I. Alexopoulou, M. Sofiadis and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2014, **53**, 13201; (f) K. Tokumaru, T. Ohfusa, S. Arai and A. J. Nishida, *J. Antibiot.*, 2016, **69**, 340; (g) S. F. Martin and P. W. Zinke, *J. Org. Chem.*, 1991, **56**, 6600; (h) B. A. Keay, *Chem. Soc. Rev.*, 1999, **28**, 209; (i) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong and H. N. C. Wong, *Tetrahedron*, 1998, **54**, 1955.
- (a) A. U. Rao, D. Xiao, X. Huang, W. Zhou, J. Fossetta, D. Lundell, F. Tian, P. Trivedi, R. Aslanian and A. Palani, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1068; (b) F. Hasegawa, K. Niidome, C. Migihashi, M. Murata, T. Negoro, T. Matsumoto, K. Kato and A. Fujii, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4266; (c) Y.-S. Li, H. Tian, D.-S. Zhao, D.-K. Hu, X.-Y. Liu, H.-W. Jin, G.-P. Song and Z.-N. Cui, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 3632; (d) S.-Y. Lee, A. Perotti, S. De Jonghe, P. Herdewijn, T. Hanck and C. E. Muller, *Bioorg. Med. Chem. Lett.*, 2016, **24**, 3157; (e) A. E. Shchekotikhin, L. G. Dezhenkova, V. B. Tsvetkov, Y. N. Luzikov, Y. L. Volodina Jr, V. V. Tatarskiy, A. A. Kalinina, M. I. Treshalina, H. M. Treshalina, V. I. Romanenko, D. N. Kaluzhny, M. Kubbutat, D. Schols, Y. Pommier, A. A. Shtil and M. N. Preobrazhenskaya, *Eur. J. Med. Chem.*, 2016, **112**, 114; (f) H. Zhong, C.-H. Wu, C.-Z. Li, J. Carpenter, C.-C. Chueh, J.-Y. Chen, H. Ade and A. K.-Y. Jen, *Adv. Mater.*, 2016, **28**, 951.
- A. Kamal, V. L. Nayak, N. Nagesh, M. V. P. S. Vishnuvardhan and N. V. S. Reddy, *Bioorg. Chem.*, 2016, **66**, 124.
- Z.-N. Cui, Y.-S. Li, D.-K. Hu, H. Tian, J.-Z. Jiang, Y. Wang and X.-J. Yan, *Sci. Rep.*, 2016, **6**, 20204.
- R. Srikanth, A. Sivarajan, C. S. Venkatesan, V. Maheshwaran, P. Sugumar, G. Rajitha, J. C. Varalakshmi and M. N. Ponnuswamy, *J. Mol. Struct.*, 2016, **1125**, 481.
- K. Ran, C. Gao, H. Deng, Q. Lei, X. You, N. Wang, Y. Shi, Z. Liu, W. Wei, C. Peng, L. Xiong, K. Xiao and L. Yu, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 3669.
- J. Kobayashi, Y. Ohizumi, H. Nakamura and Y. Hirata, *Tetrahedron Lett.*, 1986, **27**, 2113.
- J.-Q. Huo, L.-Y. Ma, Z. Zhang, Z.-J. Fan, J.-L. Zhang, T. V. Beryozkina and V. A. Bakulev, *Chin. Chem. Lett.*, 2016, **27**(9), 1547.
- (a) R. Padmavathi, R. Sankar, B. Gopalakrishnan, R. Parella and S. A. Babu, *Eur. J. Org. Chem.*, 2015, 3727; (b) M. Miao,



- Y. Luo, H. Li, X. Xu, Z. Chen, J. Xu and H. Ren, *J. Org. Chem.*, 2016, **81**, 5228.
- 11 (a) L. Peng, X. Zhang, M. Ma and J. Wang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1905; (b) V. Cadierno, J. Diez, J. Gimeno and N. Nebra, *J. Org. Chem.*, 2008, **73**, 5852; (c) J. Chen and S. Ma, *Chem.-Asian J.*, 2010, **5**, 2415; (d) P. Lenden, D. A. Entwistle and M. C. Willis, *Angew. Chem., Int. Ed.*, 2011, **50**, 10657; (e) Z.-W. Chen, M.-T. Luo, Y.-L. Wen, M. Ye, Z.-G. Zhou and L.-X. Liu, *Synlett*, 2014, **25**, 2341; (f) X. Zhang, W. Dai, W. Wu and S. Cao, *Org. Lett.*, 2015, **17**, 2708; (g) J.-T. Yu, B. Shi, H. Peng, S. Sun, H. Chu, Y. Jiang and J. Cheng, *Org. Lett.*, 2015, **17**, 3643; (h) S. Manna and A. P. Antonchick, *Org. Lett.*, 2015, **17**, 4300; (i) B. V. S. Reddy, V. V. Reddy, G. Karthik and B. Jagadeesh, *Tetrahedron*, 2015, **71**, 2572; (j) X. Cheng, Y. Yu, Z. Mao, J. Chen and X. Huang, *Org. Biomol. Chem.*, 2016, **14**, 3878; (k) L. Wang, X. Liu, M. Wang and J. Liu, *Org. Lett.*, 2016, **18**, 2162.
- 12 (a) S. Ishikawa, Y. Noda, M. Wada and T. Nishikata, *J. Org. Chem.*, 2015, **80**, 7555; (b) C. R. Reddy, S. Z. Mohammed and P. Kumaraswamy, *Org. Biomol. Chem.*, 2015, **13**, 8310.
- 13 (a) Y. Yang, M. Gao, L.-M. Wu, C. Deng, D.-X. Zhang, Y. Gao, Y.-P. Zhu and A.-X. Wu, *Tetrahedron*, 2011, **67**, 5142; (b) X. Yang, F. Hu, H. Di, X. Cheng, D. Li, X. Kan, X. Zoua and Q. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 8947.
- 14 M. Gao, Y. Yang, Y.-D. Wu, C. Deng, L.-P. Cao, X.-G. Meng and A.-X. Wu, *Org. Lett.*, 2010, **12**, 1856.

