Synthetic strategy toward furyl- and benzofuryl-containing building blocks for organic materials

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Abstract

A synthetic approach to furyl- and benzofuryl-containing building blocks utilizing easily accessible substrates is reported. Cascade acid-catalyzed reactions of 2-methylfuran with α,β-unsaturated carbonyl compounds or salicyl alcohols followed by oxidation afford functionalized furans and benzofurans, respectively. Synthetic potential of the obtained products was demonstrated by synthesizing hetaryl-substituted heterocycles, which may find an application in materials chemistry.

Keywords

furan
benzofuran
heterocycle
methodology
building block

1. Introduction

Organic molecules have an opportunity for replacing the traditional inorganic compounds in functional materials due to their low cost, flexibility in designing physical and chemical properties, and simplicity of the manufacturing processes [1, 2]. The possibility for the organic compounds to act as active components of solar cells [3], optoelectronic devices [4], sensors [5, 6] and other materials [7, 8] has been the focus of extensive research.

The functional properties of heterocyclic architectures, which have certain advantages over carbocyclic counterparts [9], have been intensively studied [10, 11]. Historically, thiophene derivatives were among the first to be used as substrates to obtain functional materials for organic electronics [12]. In turn, furans, being oxygen-containing analogs with better solubility as well as with other suitable physicochemical features [13] could compete with thiophenes; however, their use as integral parts of functional materials started to be investigated just recently. Thus, the potential applications of furans and benzofurans in photovoltaics [14–16] and optoelectronics [17, 18] are being evaluated currently with a specific focus on hetaryl-substituted systems (Figure 1).

To date, there are few general synthetic strategies toward furyl- and benzofuryl-containing heterocycles. Usually, benzofurans are accessed via transition metal-catalyzed inter- or intramolecular cyclizations of phenols or their O-protected derivatives with alkenes and alkynes [19]. Suzuki-Miyaura cross-coupling is used to obtain target heterocyclic motifs possessing both benzofuran [20] and furan [21, 22] moieties. The conjugate addition/cyclization has also been successfully utilized for the synthesis of substituted furan-indol conjugates [23]. Heterogeneous catalysis with Cu@imine/Fe3O4 nanoparticles [24], graphene oxide with cascade addition/cyclization [25] was applied to obtain complex heterocyclic molecules with furyl substituents.

Acid-catalyzed domino reaction of accessible alkylfurans [26] with ambiphilic compounds, comprehensively explored by Butin et al., serves as a convenient tool for constructing functionalized heterocyclic compounds [27]. The Butin reaction yields a wide range of heterocycles that possess alkanone fragments, including furans and benzofurans. In the present work, we propose a way for the utilization of the Butin reaction products as building blocks for construction hetaryl-substituted furans [28] and benzofurans [29] as potential functional molecules. The synthetic design relies on the possibility for the oxidation of the alkanone side chain followed by chemical engagement of the formed α,β-unsaturated ketone fragment into chemical transformations to obtain novel heterocyclic systems [30, 31, 32] (Scheme 1).
2. Experimental

$^1$H and $^{13}$C NMR spectra were recorded with a «Bruker Avance III HD 400» (400 MHz for $^1$H and 101 MHz for $^{13}$C NMR) spectrometer at room temperature; the chemical shifts (δ) were measured in ppm with respect to the solvent (CDCl$_3$, $^1$H: δ = 7.26 ppm, $^{13}$C: δ = 77.16 ppm). Coupling constants ($J$) are given in Hertz. Splitting patterns of apparent multiplets associated with an averaged coupling constants were designated as $s$ (singlet), $d$ (doublet), $t$ (triplet), $m$ (multiplet), and $b$ (broadened). GC/MS analysis was performed on an «Agilent 7890B» interfaced to an «Agilent 5977A» mass selective detector. Melting points were determined with a «Stuart SMP 30». Column chromatography was performed on silica gel Macherey Nagel (40–63 μm). Reaction progress was monitored by GC/MS analysis and thin layer chromatography (TLC) on aluminum backed plates with Merck Kiesel 60 F254 silica gel. The TLC plates were visualized either by UV radiation at a wavelength of 254 nm. All the reactions were carried out using dried and freshly distilled solvent.

2.1. General method for synthesis of furans

A 5 mL microreaction vial equipped with a stirring bar and a Teflon cap was charged with unsaturated ketone 1 (1 mmol), 2-methylfuran (2) (1.5 mmol, 123 mg, 1.5 equiv), AcOH (5 mL), and 48% aq. HBr (8.4 mg, 5.6 μL, 5% mol). The vial was closed and placed into an aluminum heating block preheated to 80 °C, and the mixture was stirred for 12 h (TLC control). Upon completion, the reaction mixture was filtered through a thin layer of silica gel. The solvent...
was evaporated, and the residue was dissolved in dichloromethane (2 mL) and DDQ (1.2 mmol, 272 mg, 1.2 equiv.) was added. The mixture was stirred at room temperature until full consumption of the starting material (TLC control). Upon completion, the reaction mixture was subjected to column chromatography on silica gel (eluent: dichloromethane/petroleum ether, 1:1).

### 2.1.1. (E)-4-(3,5-diphenylfuran-2-yl)but-3-en-2-one (3a)

Yellow needles. Yield 265 mg (92%); \( m_p = 112-113^\circ C \) (ethanol). \( R_f = 0.45 \) (petroleum ether/ethyl acetate, 3:1).

'H NMR (400 MHz, CDCl3) \( \delta 7.82-7.75 \) (m, 2H), 7.51-7.32 (m, 9H), 6.90 (s, 1H), 6.84 (d, \( J = 15.6 \) Hz, 1H), 2.34 (s, 3H) ppm. \( ^{13} \)C NMR (101 MHz, CDCl3) \( \delta 197.6, 155.7, 146.1, 134.3, 129.7, 129.1 \) (2C), 129.0 (2C), 128.9, 128.5 (2C), 128.3, 128.1, 124.6 (2C), 124.3, 108.8, 28.3 ppm. GC-LRMS (EI, \( m/z \)): 288 \( (M^+, 100\%) \), 273 \( ([M-CH_3]^+) \), 245 \( ([M-CH_3CO]^+) \).

### 2.1.2. (E)-4-(5-(4-methoxyphenyl)-3-phenylfuran-2-yl)but-3-en-2-one (3b)

Orange solid. Yield 264 mg (83%); \( m_p = 142-143^\circ C \) (ethanol). \( R_f = 0.40 \) (petroleum ether/ethyl acetate, 3:1).

'H NMR (400 MHz, CDCl3) \( \delta 7.73-7.68 \) (m, 2H), 7.50-7.37 (m, 6H), 6.98-6.94 (m, 2H), 6.79 (d, \( J = 15.8 \) Hz, 1H), 6.76 (s, 1H), 3.85 (s, 3H), 2.33 (s, 3H) ppm. \( ^{13} \)C NMR (101 MHz, CDCl3) \( \delta 197.7, 160.4, 155.9, 145.4, 134.6, 132.6, 129.1 \) (2C), 128.5 (2C), 128.3, 128.3, 126.2 (2C), 123.7, 122.6, 114.5 (2C), 107.4, 55.5, 28.1 ppm. GC-LRMS (EI, \( m/z \)): 318 \( (M^+, 100\%) \), 303 \( ([M-CH_3]^+) \), 275 \( ([M-CH_3CO]^+) \).

### 2.1.3. (E)-4-(3,5-bis(4-methoxyphenyl)furan-2-yl)but-3-en-2-one (3c)

Brown solid. Yield 261 mg (97%); \( m_p = 137-139^\circ C \) (ethanol). \( R_f = 0.28 \) (petroleum ether/ethyl acetate, 4:1).

'H NMR (400 MHz, CDCl3) \( \delta 7.73-7.68 \) (m, 2H), 7.44 (d, \( J = 15.6 \) Hz, 1H), 7.41-7.37 (m, 2H), 7.02-6.93 (m, 4H), 6.77 (d, \( J = 15.6 \) Hz, 1H), 6.73 (s, 1H), 3.86 (s, 3H), 3.858 (s, 3H), 2.32 (s, 3H) ppm. \( ^{13} \)C NMR (101 MHz, CDCl3) \( \delta 197.6, 160.4, 155.9, 145.2, 134.5, 129.8 \) (2C), 128.4, 126.27 (2C), 125.1, 123.3, 122.8, 114.7 (2C), 114.6 (2C), 107.5, 55.5 (2C), 28.1 ppm. GC-LRMS (EI, \( m/z \)): 348 \( (M^+, 100\%) \), 333 \( ([M-CH_3]^+) \), 305 \( ([M-CH_3CO]^+) \).

### 2.2. General method for synthesis of benzofurans

To a solution of salicylalcohol 4 (0.5 mmol) in dichloroethane (2 mL) was added 2-methylfurans 2 (0.75 mmol, 61.5 mg, 1.5 equiv.) and trifluoromethanesulfonic acid (0.05 mmol, 7.5 mg, 0.1 equiv.). The resulting mixture was stirred at 80°C until full consumption of the starting material (TLC control, ca. 1 h). Upon completion, the reaction mixture was filtered through a thin layer of silica gel, and DDQ (0.6 mmol, 136 mg, 1.2 equiv.) was added. The mixture was stirred at room temperature until full consumption of the starting material (TLC control). Upon completion, the reaction mixture was subjected to column chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 1:20).
128.5 (2C), 127.5, 127.3 (2C), 126.7, 125.3, 124.9, 123.8 (2C), 121.8, 114.0, 106.8, 28.1 ppm. GC-LRMS (EI, m/z): 327 (M⁺, 100%), 312 ([M⁺ − CH₃]⁺), 284 ([M⁺ − CH₃CO]⁺).

2.3.2. 1-(4-(3-phenylbenzofuran-2-yl)-1H-pyrrol-3-yl)ethan-1-one (7)
Colorless oil. Yield 114 mg (95%). Rf = 0.33 (petroleum ether/ethyl acetate, 1:1). 1H NMR (400 MHz, CDCl₃) δ 9.42 (br. s, 1H), 7.56–7.50 (m, 1H), 7.38–7.33 (m, 1H), 7.33–7.27 (m, 2H), 7.25–7.09 (m, 6H), 6.58–6.51 (m, 1H), 2.10 (s, 3H) ppm. 13C NMR (101 MHz, CDCl₃) δ 193.9, 154.7, 146.9, 133.1, 129.2 (2C), 128.9, 128.7 (2C), 127.1, 125.8, 124.6, 124.5, 122.9, 122.0, 120.1, 119.0, 113.7, 111.4, 28.3 ppm. GC-LRMS (EI, m/z): 301 (M⁺, 100%), 286 ([M⁺ − CH₃]⁺), 258 ([M⁺ − CH₃CO]⁺).

3. Results and discussion
We began our research with evaluating the possibility of synthesizing the target α,β-unsaturated carbonyl compounds with furyl substituent at β-position. To this end, we utilized a recently reported acid-catalyzed domino reaction of 2-methylfuran (2) with unsaturated ketones 1 that led to the formation of furylalkanones A (Scheme 2). We screened various oxidants in order to obtain respective unsaturated products 3 from alkanones A [34–36] and found that DDQ in the amount of 1.2 equiv. effectively induced the desired transformation affording compounds 3 with high yields. The oxidation step could be coupled with the acid-catalyzed domino reaction with the only requirement to change the solvent after passing the initial reaction mixture through a pad of silica gel. The developed method was evaluated by synthesizing three examples of the target molecular architecture.

In order to obtain the target benzofuryl-containing unsaturated ketones 5, we employed another acid-catalyzed domino reaction, namely, a reaction of salicyl alcohols 4 with 2-methylfuran (2) [29] (Scheme 3). The oxidative conditions found for the synthesis of compounds 3 from alkanone intermediates appeared to be suitable for obtaining the benzofuran counterparts 5. The oxidation step was also integrated into the process without the need to switch the solvent, and the resulting products 5a–c were obtained with high yields.

The presence of a highly reactive α,β-unsaturated ketone fragment in the structure of the synthesized compounds opens prospect for applying the products 3 and 5 as building blocks for obtaining the furyl- and benzofuryl-containing heterocycles. To demonstrate this possibility, we performed the reaction of the compounds 3a and 5a with TosMIC upon activation with a base [37–40]. The reaction afforded respective pyrroles 6 and 7 with high yields (Scheme 4). The structure of the compounds 6 and 7 represents a general furyl/benzofuryl-substituted heterocyclic motif. Importantly, well-explored chemical behaviour of the acetyl group and free pyrrolic nitrogen possessed by the final compounds could be utilized for further structural modifications.
4. Conclusions

We developed a protocol for the synthesis of functionalized furans and benzofurans starting from easily available precursors. The obtained products could serve as building blocks for designing potential furan- and benzofuran-based heterocyclic functional molecules for organic electronics.

Supplementary materials

No supplementary materials are available.

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Conflict of interest

The authors declare no conflict of interest.

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References

1. Kumar B, Kaushik BK, Negi YS. Organic thin film transistors: structures, models, materials, fabrication, and applications. a review. Polym Rev. 2014;54(1):33–111. doi:10.1080/05807224.2013.848455

2. Tsang MP, Sonnemann GW, Bassani DM. Life-cycle assessment of cradle-to-grave opportunities and environmental impacts of organic photovoltaic solar panels compared to conventional technologies. Sol Energy Mater Sol Cells. 2016;156:37–48. doi:10.1016/j.solmat.2016.04.024

3. Cao W, Jiangeng X. Recent progress in organic photovoltaics: device architecture and optical design. Energy Environ Sci. 2014;7(7):2123–2144. doi:10.1039/c4ee00250a

4. Dong J, Chuxuan Y, Yingzhi C, Wenjie Z, Yushuan P, Yue Z, Luning W, Zhenghong H. Organic semiconductor nanostructures: optoelectronic properties, modification strategy, and photocatalytic applications. J Mater Sci Technol. 2021;113:175–198. doi:10.1016/j.jmst.2021.09.002

5. Gonçalves JM, Martins PR, Rocha DP, Matias TA, Julião MS, Muñoz RA, Angnes L. Recent trends and perspectives in electrochemical sensors based on MOF-derived materials. J Mater Chem C. 2021;9:8718–8745. doi:10.1039/D1TC00252K

6. Yang D, Ma D. Development of organic semiconductor photodetectors: from mechanism to applications. Adv Opt Mater. 2018;7(1):1800522. doi:10.1002/adom.201800522

7. Marin ML, Santos-Juanes L, Arques A, Amat AM, Miranda MA. Organic photocatalysts for the oxidation of pollutants and model compounds. Chem Rev. 2011;112(3):1710–1750. doi:10.1021/cr200054z

8. Ates B, Koytepe S, Ulu A, Gurses C, Thakur VK. Chemistry, structures, and advanced applications of nanocomposites from biorenewable resources. Chem Rev. 2020;120(17):9304–9362. doi:10.1021/acs.chemrev.9b00553

9. Wang C, Dong H, Hu W, Liu Y, Zhu D. Semiconducting π-conjugated systems in field-effect transistors: a material odyssey of organic electronics. Chem Rev. 2011;112(12):2208–2267. doi:10.1021/cr100380z

10. Mei J, Diao Y, Appleton AL, Fang L, Bao Z. Integrated materials design of organic semiconductors for field-effect transistors. J Am Chem Soc. 2013;135(18):6724–6746. doi:10.1021/ja400881m

11. Zhang F, Xu X, Tang W, Zhang J, Zhuo Z, Wang J, Wang Y. Recent development of the inverted configuration organic solar cells. Sol Energy Mater Sol Cells. 2011;95(7):1785–1799. doi:10.1016/j.solmat.2011.02.002

12. Perepichka IF, Perepichka DF. Handbook of thiophene-based materials. New York: John Wiley & Sons; 2009. 833 p. doi:10.1002/0470745533

13. Zheng B, Huo L. Recent advances of furan and its derivatives based semiconductor materials for organic photovoltaics. Small Methods. 2021;5(9):2100493. doi:10.1002/smtd.202100493

14. Woo CH, Beaujuge PM, Holcombe TW, Lee OP, Fréchet JMJ. Incorporation of furan into low band-gap polymers for efficient solar cells. J Am Chem Soc. 2010;132(44):15547–15549. doi:10.1021/ja108115y

15. Song C, Sun D, Peng X, Bai J, Zhang R, Hou S, Xu Z. Dimerization of cyclopropenes to bifurans using tandem metal relay chemistry. Chem Commun. 2013;49(80):9167–9169. doi:10.1039/C3CC44262F

16. Nazim M, Ameen S, Akhter MS, Seo HK, Shin HS. Furan-bridged thiazole [5,4-d]thiazole based D–π–A–D type linear chromophore for solution-processed bulk-heterojunction organic solar cells. RSC Adv. 2015;5(9):6286–6293. doi:10.1039/C4RA13563A

17. Ramkumar V, Kannan P. Thiophene and furan containing pyrazoline luminescent materials for optoelectronics. J Lumin. 2016;169:204–215. doi:10.1016/j.jlumin.2015.09.020

18. Sun W, Wang C-H, Lv S-F, Jiang JX, Guo X, Zhang F. Bis(benzofuran)pyrrole and hybrid thienopyrrole derivatives for organic thin-film transistors. Org Electron. 2019;77:105548. doi:10.1016/j.orgel.2019.105548

19. Chiumento L, D’Orsi R, Funicello M, Lapatelli F. Last decade of unconventional methodologies for the synthesis of substituted benzofurans. Mol. 2020;25(10):2527. doi:10.3390/molecules25102527
20. Hussain M, Thai Hung N, Abbas N, Khera RA, Malik I, Patonay T, Langer P. Synthesis of arylated benzofurans by regioselective Suzuki-miyaura cross-coupling reactions of 2,3-dibromobenzofuran- and 2,3,5-tri bromobenzofurans. J Heterocycl Chem. 2014;52(2):497–505. doi:10.1002/jhet.2085

21. Cui K, Gao M, Zhao H, Zhang D, Van H, Huang H. An efficient synthesis of aryl-substituted pyroles by the suzuki-miyaura coupling reaction of SEM-protected pyroles. Mol. 2019;24(8):1594. doi:10.3390/molecules24081594

22. Brucoli F, Guzman JD, Maitra A, James CH, Fox KR, Bhakta S. Synthesis, anti-mycobacterial activity and dna sequence-selectivity of a library of biaryl-motifs containing polyamides. Bioorg Med Chem. 2015;23(13):3705–3711. doi:10.1016/j.bmc.2015.04.001

23. Yang Y, Gao M, Wu LM, Deng C, Zhang DX, Gao Y, Wu AX. A facile synthesis of indole-furan conjugates via integration of convergent and linear domino reactions. Tetrahedron. 2011;67(29):5142–5149. doi:10.1016/j.tet.2011.04.058

24. Thwin M, Mahmoudi B, Ivashchuk OA, Yousif QA. An efficient and recyclable nanocatalyst for the green and rapid synthesis of biologically active polysubstituted pyroles and 1,2,4,5-tetrasubstituted imidazole derivatives. RSC Adv. 2019;9(28):15966–15975. doi:10.1039/c9ra02325a

25. Jana A, Das Adhikary N, Pramanik A. Graphene oxide (GO) catalysed MW-assisted one-pot synthesis of densely substituted furan. Green Chem. 2020;22:4304–4310. doi:10.1039/dog000723d

26. Serrano-Ruiz JC, Luque R, Sepulveda-Escribano A. Transformations of biomass-derived platform molecules: from high added-value chemicals to fuels via aqueous-phase processing. Chem Soc Rev. 2011;40(11):5266–5281. doi:10.1039/c1cs15131b

27. Aabaev VT, Trushkov IV, Uchuskin MG. The butin reaction. Heterocycl Compd. 2016;52(12):973–995. doi:10.1007/s10551-017-1906-x

28. Fadeev AA, Makarov AS, Uchuskin MG. Acid-catalyzed cascade reaction of 2-alkylfurans with α,β-unsaturated ketones: a shortcut to 2,3,5-trisubstituted furans. J Org Chem. 2021;86(23):17362–17370. doi:10.1021/acs.joc.0c01692

29. Makarov AS, Kekhvaeva AE, Chalikidki PN, Aabaev VT, Trushkov IV, Uchuskin MG. A simple synthesis of densely substituted benzo[6]furans by domino reaction of 2-hydroxybenzyl alcohols with 2-substituted furans. Synthesis. 2019;51(19):3747–3757. doi:10.1055/s-0039-1690000

30. Albuquerque HMT, Santos CMM, Cavaleiro JAS, Silva AMS. Chalcones as versatile synthons for the synthesis of 5- and 6-membered nitrogen heterocycles. Curr Org Chem. 2014;18(21):2750–2773. doi:10.2174/18722032114180002753

31. Bagdi A, Pattanayak P, Paul S, Mitra M, Choudhuri T, Sheikh AS. Application of conjugated carbonyls in the synthesis of heterocycles via oxidative cycloaddition and cyclization reactions. Adv Synth Catal. 2020;362(24):5601–5621. doi:10.1002/adsc.202000970

32. Kuznetsov AN, Makarov AS, Rubtsov AE, Butin AV, Gevorgyan V. Brønsted acid-catalyzed one-pot synthesis of indoles from O-aminobenzyl alcohols and furans. J Org Chem. 2013;78(23):12144–12153. doi:10.1021/jo402122p

33. Merkushnev AA, Strel'nikov VN, Uchuskin MG, Trushkov IV. A simple synthesis of benzo[6]furans by acid-catalyzed domino reaction of salicyl alcohols with 4-toluenesulfonylfuranlylamine. Tetrahedron. 2017;73(46):6523–6529. doi:10.1016/j.tet.2017.09.043

34. Chen H, Liu L, Huang T, Chen J, Chen T. Direct dehydrogenation for the synthesis of α,β-unsaturated carbonyl compounds. Adv Synth Catal. 2020;362(16):3332–3346. doi:10.1002/adsc.202000454

35. Alsharif MA, Raja QA, Majeed NA, Jassas RS, Alsimarye AA, Sadiq A, Naeem N, Mughal EU, Alsantali RI, Moussa Z, Ahmed SA. DDQ as a versatile and easily recyclable oxidant: a systematic review. RSC Adv. 2021;11:29826. doi:10.1039/d1ra04575i

36. Walker D, Hiebert JD. 2,3-dichloro-5,6-dicyanobenzoquinone and its reactions. Chem Rev. 1967;67(2):153–195. doi:10.1021/cr60246a002

37. Mathiyazhagan AD, Anilkumar G. Recent advances and applications of p-toluenesulfonylmethyl isocyanide (TosMIC). Org Biomol Chem. 2019;17:6735–6747. doi:10.1039/c9ob00847k

38. Ma Z, Ma Z, Zhang D. Synthesis of multi-substituted pyrrole derivatives through [3+2] cycloaddition with tosylmethyl isocyanides (TosMICs) and electron-deficient compounds. Mol. 2018;23(10):2866. doi:10.3390/molecules23102866

39. Kaur T, Wadhwa P, Sharma A. Arylsulfonylmethyl isocyanides: a novel paradigm in organic synthesis. RSC Adv. 2015;5(65):52769–52787. doi:10.1039/c5ra0786h

40. Kumar K. TosMIC: A powerful synthon for cyclization and sulfonylation. Chem Sel. 2020;5(33):10298–10328. doi:10.1002/ckls.2020001344