



Cite this: *RSC Adv.*, 2022, 12, 30426

Selective synthesis of 3-formylbenzofuran and 3-acylbenzofuran using a chalcone rearrangement strategy†

Akira Nakamura,^{ID} Akira Imamiya, Yuichiro Ikegami, Fei Rao, Harumi Yuguchi, Yasuyoshi Miki and Tomohiro Maegawa^{ID}*

Received 27th September 2022
Accepted 13th October 2022

DOI: 10.1039/d2ra06080a

rsc.li/rsc-advances

We developed a method for highly selective synthesis of two benzofuran isomers, by rearranging and subsequently transforming 2-hydroxychalcones. Depending on the reaction conditions, synthesis of 3-formylbenzofurans, unconventional products, and 3-acylbenzofurans was achieved through cyclized 2,3-dihydrobenzofurans obtained from the rearranged products. The facile synthesis of 3-formylbenzofurans facilitated synthesis of the natural product, puerariafuran, from the corresponding chalcone.

Introduction

Benzofuran and its derivatives are present as scaffolds in many natural products and biologically active compounds.¹ These compounds have attracted much attention in the pharmaceutical and pesticide industries because of their promising anti-bacterial, antimicrobial, antitumor, and antidiabetic activities.² Hence, the synthesis of benzofurans has aroused considerable interest and various methodologies have been reported and applied for the synthesis of natural products.³

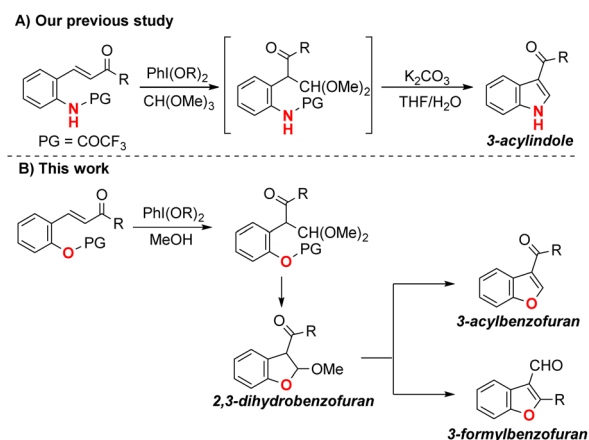
Our current research focuses on the development of methods for synthesizing various heterocycles used for the rearrangement of chalcones.⁴ Combination of chalcones and rearrangement reactions has been reported, but has limited utility for the construction of isoflavones.⁵ We also reported the synthesis of pterocarpin *via* isoflavones, through hypervalent iodine-mediated oxidative rearrangement of 2,2'-hydroxychalcone derivatives. In this study, we found that 3-acylbenzofuran was formed from 2-hydroxychalcone derivatives.^{4b} The synthesis of 3-acylbenzofurans is an unexplored topic; little is known about routes to effective synthesis. For example, Friedel-Crafts acylation of benzofurans results in low C2/C3 regioselectivity,⁶ and most existing methods can synthesize 3-acylbenzofurans with substituents at the C2 position.⁷

We recently developed a method for concise one-pot synthesis of 3-acylindoles. This method first rearranges the *N*-COCF₃-protected 2-aminochalcone with phenyliodine diacetate (PhI(OAc)₂); 3-acylindoles are then produced under basic conditions *via* deprotection and a cyclization reaction

(Scheme 1A).^{4c} To apply the chalcone-rearrangement strategy for the synthesis of 3-acylbenzofurans, we investigated the reaction of the protected 2-hydroxychalcone. Unexpectedly, our approach produced not only 3-acylbenzofuran, but also 3-formylbenzofuran (with high selectivity) from 2,3-dihydrobenzofuran (Scheme 1B).

Results and discussion

We started by testing the rearrangement conditions using 2-hydroxychalcone **1** with a hypervalent iodine reagent (Scheme 2). No rearrangement product **2** was obtained without the protecting group (R = H). Attempts were made to synthesize chalcones protected with the trifluoroacetyl group used in our previous indole synthesis, but the chalcones were unstable and

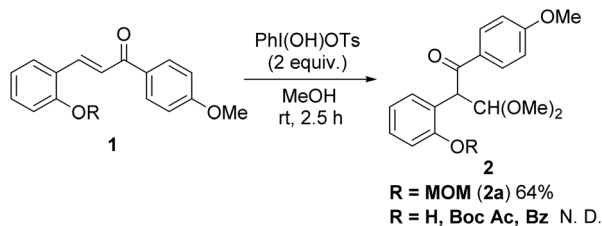


Scheme 1 Chalcone rearrangement strategies for synthesis of heterocycles.

School of Pharmaceutical Sciences, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan. E-mail: maegawa@phar.kindai.ac.jp

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d2ra06080a>





Scheme 2 Rearrangement of protected chalcone 1.

could not be isolated. Then, the reaction was evaluated with chalcones bearing various protecting groups, such as *t*-butoxycarbonyl (Boc), acetyl (Ac) and benzoyl (Bz), but no rearranged products were obtained. The desired product was obtained with methoxymethyl (MOM) protection. The reaction of MOM-protected hydroxychalcone with two equivalents of hydroxy(tosyloxy)iodobenzene (PhI(OH)OTs) gave the corresponding rearranged product **2a** in 64% yield.

We next examined deprotection followed by simultaneous cyclization to the corresponding 3-acylbenzofuran under acidic conditions (Table 1). With excess AcOH, no reaction was observed, even with reflux (entry 1). The desired benzofuran **4a** was not obtained using trifluoroacetic acid (TFA), whereas 2,3-dihydrobenzofuran **3a**, the precursor of **4a**, was isolated in 56% yield (entry 2). The use of *p*-toluenesulfonic acid (*p*-TsOH) increased the yield of **3a** slightly to 62% (entry 3), but **3a** was not obtained, and nor was **4a** with heating (entry 4). The use of the solvents CH₂Cl₂, THF, and MeOH did not yield the desired **4a**. We finally optimized the conditions to obtain **3a** in 80% yield using 0.1 equivalent of *p*-TsOH (entry 5).

Subsequently, the transformation of 2,3-dihydrobenzofuran **3a** into **4a** was studied under basic and acidic conditions (Table 2). When the reaction was performed using K₂CO₃, aromatization proceeded at room temperature affording 3-acylbenzofuran **4a** in 97% yield (entry 1). Pyridine was

Table 1 The transformation of **2a** under acidic conditions^a

Entry	Acid	X [equiv.]	Temp. [°C]	Time [h]	Yield ^b [%]
1	AcOH	5	80	12	—
2	TFA	1	r.t.	3	56
3	<i>p</i> -TsOH	1	r.t.	0.5	62
4	<i>p</i> -TsOH	1	80	0.5	—
5	<i>p</i> -TsOH	0.1	r.t.	2	80

^a The reactions were performed with **2a** (0.2 mmol) in 2 ml of solvent.

^b Isolated yield.

Table 2 The transformation of **3a** to benzofurans^a

Entry	Reagent	Solvent	Temp. [°C]	Time [h]	Yield ^b [%]
1	K ₂ CO ₃	THF	r.t.	4	97
2	Pyridine	THF	70	12	Trace
3	—	AcOH	110	3	98
4	PPTS	PhCH ₃	110	7	95
5	TFA	PhCH ₃	110	4	95
6	<i>p</i> -TsOH	(CF ₃) ₂ CHOH	r.t.	0.5	98

^a The reactions were performed with **2a** (0.2 mmol) in 2 ml of solvent.

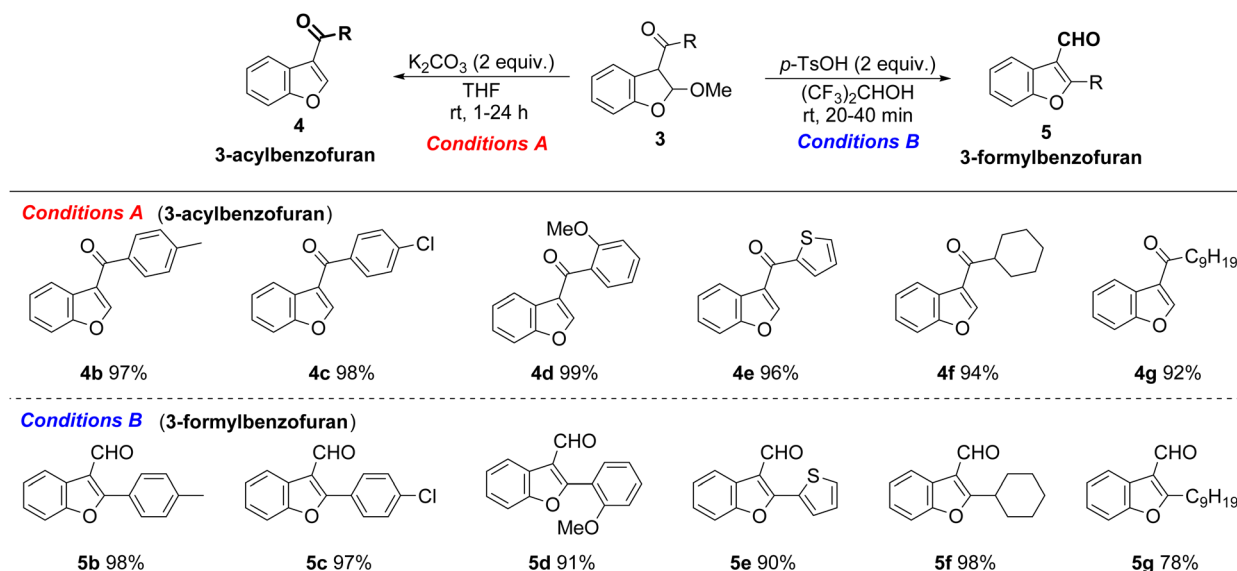
^b Isolated yield.

ineffective and only trace amounts of **4a** were obtained upon reflux (entry 2). However, **4a** was obtained in 98% yield in AcOH (entry 3). Other acids (pyridinium *p*-toluenesulfonate (PPTS) and TFA) in toluene also gave **4a** in high yields under reflux conditions (entries 4 and 5). Surprisingly, unexpected formation of 3-formylbenzofuran **5a** was observed with *p*-TsOH when 1,1,1,3,3,3-hexafluoro-2-propanol was used as a solvent. 3-Formylbenzofurans are found in the skeletons of natural products,⁸ and few synthetic methods are known.⁹

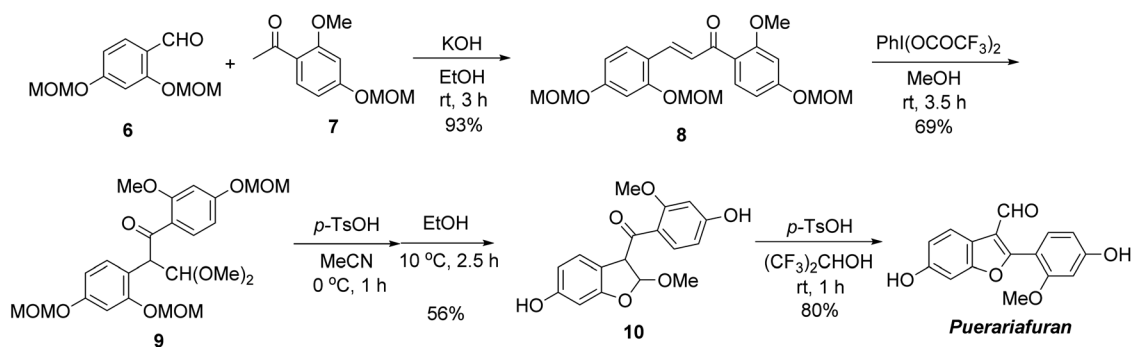
On optimizing the conditions for the selective synthesis of benzofuran isomers, the transformation was extended to various 2,3-dihydrobenzofurans **3** with aryl or alkyl groups on the ketone moiety (Table 3). A series of electron-donating groups (*e.g.*, *p*-methyl and *o*-methoxy) and electron-withdrawing substituents (*e.g.*, *p*-chloro) on the phenyl ring reacted smoothly to give the respective 3-acylbenzofurans (**4b–4d**) and 3-formylbenzofuran (**5b–5d**) in excellent yields. The reaction with 2,3-dihydrobenzofuran with a thiophenyl group afforded **4e** and **5e** in yields of 96% and 90%, respectively. During the transformation of **3f** and **3g** with alkyl groups, 3-acylbenzofurans (**4f** and **4g**) and 3-formylbenzofuran **5f** were obtained in high yields, whereas the yield of 3-formylbenzofuran **5g** was decreased slightly.

Next, we applied this novel 3-formylbenzofuran synthesis method to natural products (Scheme 3). Puerariafuran was chosen as the synthetic target, as it exhibits biological activities such as the inhibition of advanced glycation end products (AGEs).^{8g} Recently, Lin *et al.* synthesized puerariafuran,¹⁰ but the number of steps and total yield could be improved. First, chalcone **8** was prepared by condensing MOM-protected aldehyde **6** and acetophenone **7** in 93% yield. Oxidative rearrangement with hypervalent iodine reagent was achieved by [bis(trifluoroacetoxy)iodo]benzene (PhI(OCOCF₃)₂), affording **9** in 69% yield. To synthesize 2,3-dihydrobenzofuran **10**, we attempted to perform simultaneous deprotection and cyclization reactions under acidic conditions. Partial decomposition



Table 3 Substrate scope of selective benzofuran synthesis^a

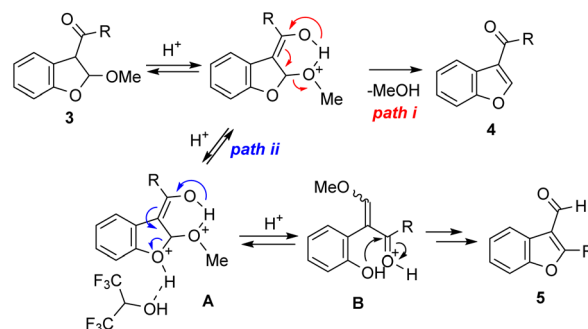
^a Reaction conditions: conditions A, K₂CO₃ (2 equiv.), THF (0.1 M). Conditions B, *p*-TsOH (2 equiv.), (CF₃)₂CHOH (0.1 M).



Scheme 3 Synthesis of puerariafuran.

was observed as the reaction progressed, but adding an excess of EtOH suppressed the decomposition and dihydrobenzofuran **10** was obtained in 56% yield.¹¹ Final conversion to the 3-formylbenzofuran skeleton was achieved on treatment with *p*-TsOH in (CF₃)₂CHOH, giving puerariafuran in 80% yield. Our protocol for puerariafuran synthesis has seven steps and an overall yield of 18% from commercial aldehyde and acetophenone; it is more efficient than the previous synthesis method (11 steps and 5.3% total yield).

The reaction mechanism for obtaining two types of benzofuran from 2,3-dihydrobenzofurans **3** under acidic conditions was thought to be as follows (Scheme 4). Using relatively weak acids, 3-acylbenzofurans **4** were obtained *via* aromatization in association with methanol elimination (path i). The mechanism of 3-formylbenzofuran **5** formation is *via* a diprotonated intermediate **A** (path ii),¹² which is stabilized with (CF₃)₂CHOH.^{13,14} Subsequent THF ring opening of intermediate **A** gives **B**, and the ring-closure at the ketone moiety then lead to **5** after



Scheme 4 Possible reaction mechanism.

aromatization and hydrolysis. According to Zanatta,¹⁵ another possible pathway for the formation of **5** is isomerization from **4**. However, the reaction of **4** with *p*-TsOH and some MeOH in (CF₃)₂CHOH resulted in no reaction.¹⁶



Conclusions

In summary, we developed a new method for highly selective synthesis of two benzofuran isomers based on rearrangement of the MOM-protected 2-hydroxychalcone. The key intermediates, 2,3-dihydrobenzofurans, could be selectively transformed into different benzofuran isomers using different reaction conditions. 3-Acylbenzofurans were obtained under basic or weakly acidic conditions in THF. Using $(\text{CF}_3)_2\text{CHOH}$ as a solvent with *p*-TsOH generated 3-formylbenzofurans selectively. A variety of 2,3-dihydrobenzofurans were selectively converted into benzofuran isomers in high yields, and the efficient total synthesis of puerariafuran proves the practicality of this method. Currently, we are developing this methodology for application to other heterocycles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by JSPS KAKENHI Grant No. 19K16329 and 18K05132, and also supported by 2021 Kindai University Research Enhancement Grant (KD2106). We also thank the Kindai University Joint Research Center for use of their facilities.

Notes and references

- (a) A. Radadiya and A. Shah, Bioactive Benzofuran Derivatives: An Insight on Lead Developments, Radioligands and Advances of the Last Decade, *Eur. J. Med. Chem.*, 2015, **97**, 356; (b) Y. Miao, Y. Hu, J. Yang, T. Liu, J. Sun and X. Wang, Natural Source, Bioactivity and Synthesis of Benzofuran Derivatives, *RSC Adv.*, 2019, **9**, 27510.
- (a) H. K. Shamsuzzaman, Bioactive Benzofuran Derivatives: A Review, *Eur. J. Med. Chem.*, 2015, **97**, 483; (b) R. J. Nevagi, S. N. Dighe and S. N. Dighe, Biological and Medicinal Significance of Benzofuran, *Eur. J. Med. Chem.*, 2015, **97**, 561; (c) Z. Xu, S. Zhao, Z. Lv, L. Feng, Y. Wang, F. Zhang, L. Bai and J. Deng, Benzofuran Derivatives and their Anti-tubercular, Anti-bacterial Activities, *Eur. J. Med. Chem.*, 2019, **162**, 266.
- (a) M. M. Heravi, V. Zadsirjan, H. Hamidi and P. H. T. Amiri, Total Synthesis of Natural Products Containing Benzofuran Rings, *RSC Adv.*, 2017, **7**, 24470; (b) L. Chiummiento, R. D'Orsi, M. Funicello and P. Lupattelli, Last Decade of Unconventional Methodologies for the Synthesis of Substituted Benzofurans, *Molecules*, 2020, **25**, 2327.
- (a) Y. Miki, S. Kobayashi, N. Ogawa and H. Hachiken, Reaction of Chalcone with Phenyliodine(III) Bis(trifluoroacetate) (PIFA): Synthesis of (\pm) -Homopterocarpin, *Synlett*, 1994, 1001; (b) Y. Miki, R. Fujita and K. Matsushita, Oxidative Rearrangement of Pentaalkoxychalcones with Phenyliodine(III) Bis(trifluoroacetate) (PIFA): Synthesis of (\pm) -10-Bromopterocarpin and (\pm) -Pterocarpin, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2533; (c) A. Nakamura, S. Tanaka, A. Imamiya, R. Takane, C. Ohta, K. Fujimura, T. Maegawa and Y. Miki, Synthesis of 3-Acylindoles by Oxidative Rearrangement of 2-Aminochalcones Using a Hypervalent Iodine Reagent and Cyclization Sequence, *Org. Biomol. Chem.*, 2017, **15**, 6702; (d) A. Nakamura, R. Takane, J. Tanaka, J. Morimoto and T. Maegawa, Construction of Azaisoflavone Derivatives by Hypervalent Iodine Reagent-Mediated Oxidative Rearrangement of 2'-Nitrochalcone, *Heterocycles*, 2018, **97**, 785.
- (a) L. Farkas, A. Gottsegen, M. Nogradi and S. Antus, Synthesis of Sophorol, Violanone, Lonchocarpin, Claussequinone, Philenopteran, Leiocalycin, and Some Other Natural Isoflavonoids by the Oxidative Rearrangement of Chalcones with Thallium(III) Nitrate, *J. Chem. Soc., Perkin Trans. 1*, 1974, 305; (b) R. V. Suresh, C. S. Rukmani Iyer and P. R. Iyer, Thallium(III) Nitrate Mediated Synthesis of Erythrinin-A, Dihydropyrano- and Pyranisoflavones, *Heterocycles*, 1985, **23**, 859; (c) R. V. Suresh, C. S. Rukmani Iyer and P. R. Iyer, A Naturally Occurring Pyranisoflavone, *Tetrahedron*, 1985, **41**, 2479; (d) M. Tsukayama, Y. Kawamura, H. Tamaki and T. Horie, Synthesis of Parvisoflavones A and B, *Chem. Pharm. Bull.*, 1991, **39**, 1704; (e) Y. Kawamura, M. Maruyama, T. Tokuoka and M. Tsukayama, Synthesis of Isoflavones from 2'-Hydroxychalcones Using Poly[4-(diacetoxy)iodyl]styrene or Related Hypervalent Iodine Reagent, *Synthesis*, 2002, **17**, 2490; (f) M. M. Hossain, Y. Kawamura, K. Yamashita and M. Tsukayama, Microwave-Assisted Regioselective Synthesis of Natural 6-Prenylpolyhydroxyisoflavones and their Hydrates with Hypervalent Iodine Reagents, *Tetrahedron*, 2006, **62**, 8625; (g) R. S. Khupse and P. W. Erhardt, Practical Synthesis of Lespedezol A₁, *J. Nat. Prod.*, 2008, **71**, 275; (h) S. Tamura, K. Yoshihira, M. Tokumaru, X. Zisheng and N. Murakami, Inhibitors for Expression of IgE Eceptor on Human Mast Cell from Puerariae Flos, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3872; (i) S. Sato and H. Ishikawa, Total Synthesis of Two Isoflavone Bis-C-glycosides: Genistein and Orobol 6,8-di-C- β -D-Glucopyranosides, *Synthesis*, 2010, **18**, 3126; (j) K. H. Almabruk, J. H. Chang and T. Mahmud, Total Synthesis of (\pm) -Isoperbergins and Correction of the Chemical Structure of Perbergin, *J. Nat. Prod.*, 2016, **79**, 2391.
- (a) V. Morizur, D. Hector, S. Olivero, J. R. Desmurs and E. Dunach, Metal Sulfonate Polymers as Catalysts for the Heterogeneous Acylation of Aromatic Derivatives, *Eur. J. Org. Chem.*, 2016, 3126; (b) Only one example for selective C3-acylation in ionic solvent; P. H. Tran, H. T. Nguyen, P. E. Hansen and T. N. Le, An Efficient and Green Method for Regio- and Chemo-Selective Friedel-Crafts Acylations Using a Deep Eutectic Solvent ([CholineCl][ZnCl₂]₃), *RSC Adv.*, 2016, **6**, 37031; (c) I. Komoto, J. Matsuo and S. Kobayashi, Catalytic Friedel-Crafts Acylation of Heteroaromatics, *Top. Catal.*, 2002, **19**, 43.
- For selected examples, see (a) H. Yuan, K.-J. Bi, B. Li, R.-C. Yue, J. Ye, Y.-H. Shen, L. Shan, H.-Z. Jin, Q.-Y. Sun and W.-D. Zhang, Construction of 2-Substituted-3-



- functionalized Benzofurans via Intramolecular Heck Coupling: Application to Enantioselective Total Synthesis of Daphnodorin B, *Org. Lett.*, 2013, **15**, 4742; (b) H. Hammoud, Q. Zhao and L. Desaubry, Synthesis of Hydroxybenzofurans by Condensation of Quinones with Benzoylacetone: Revised Structure of the Adducts, *Tetrahedron Lett.*, 2016, **57**, 4044; (c) M. Begala, P. Caboni, M. J. Matos and G. L. Delogu, Unexpected One-Step Synthesis of 3-Benzoyl-2-phenylbenzofurans under Wittig Conditions, *Tetrahedron Lett.*, 2018, **59**, 1711; (d) W. Huang, J. Xu, C. L., Z. Chen and Y. Gu, Lewis Acid-Catalyzed Synthesis of Benzofurans and 4,5,6,7-Tetrahydrobenzofurans from Acrolein Dimer and 1,3-Dicarbonyl Compounds, *J. Org. Chem.*, 2019, **84**, 2941; (e) P. Natho, L. A. T. Allen, A. J. P. White and P. J. Parsons, Transition-Metal-Free Access to Heteroaromatic-Fused 4-Tetralones by the Oxidative Ring Expansion of the Cyclobutanol Moiety, *J. Org. Chem.*, 2019, **84**, 9611; (f) L. Wang, Y. Zhang, M. Zhang, P. Bao, X. Lv, H.-G. L., X. Zhao, J.-S. Li, Z. Luo and W. Wei, Metal-Free I_2O_5 -Mediated Oxidative Synthesis of Sulfonylated Benzofurans through Cyclization Reaction of 1,6-Enynes and Arylsulfonylhydrazides, *Tetrahedron Lett.*, 2019, **60**, 1845.
- 8 (a) M. A. Ferreira, M. Moir and R. H. Thomson, New pterocarpenes from *Brya ebenus*, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2429; (b) M. Halabalaki, N. Aliannis, Z. Papoutsis, S. Mitakou, P. Moutsatsou, C. Sekeris and A. L. Skaltsounis, Three New Arylobenzofurans from *Onobrychis ebenoides* and Evaluation of Their Binding Affinity for the Estrogen Receptor, *J. Nat. Prod.*, 2000, **63**, 1672; (c) J. Takashima, S. Asano and A. Ohsaki, *Planta Med.*, 2002, **68**, 621; (d) H. Tanaka, T. Oh-Uchi, H. Etoh, M. Sako, M. Sato, T. Fukai and Y. Tateishi, An Arylbenzofuran and Four Isoflavonoids from the Roots of *Erythrina Poeppigiana*, *Phytochemistry*, 2003, **63**, 597; (e) H. Tanaka, M. Hirata, H. Etoh, M. Sako, M. Sato, J. Murata, H. Murata, D. Darnaedi and T. Fukai, Six New Constituents from the Roots of *Erythrina Variegata*, *Chem. Biodiversity*, 2004, **1**, 1101; (f) D. S. Jang, J. M. Kim, Y. M. Lee, Y. S. Kim, J.-H. Kim and J. S. Kim, Puerariafuran, a New Inhibitor of Advanced Glycation End Products (AGEs) Isolated from the Roots of *Pueraria Lobate*, *Chem. Pharm. Bull.*, 2006, **54**, 1315; (g) M. Halabalaki, X. Alexi, N. Aliannis, M. N. Alexis and A. L. Skaltsounis, Ebenfurans IV–VIII from *Onobrychis Ebenoides*: Evidence that C-Prenylation is the Key Determinant of the Cytotoxicity of 3-Formyl-2-arylbenzofurans, *J. Nat. Prod.*, 2008, **71**, 1934; (h) P. H. Nguyen, T. N. A. Nguyen, T. T. Dao, H. W. Kang, D. T. Ndinteh, J. T. Mbafor and W. K. Oh, AMP-Activated Protein Kinase (AMPK) Activation by Benzofurans and Coumestans Isolated from *Erythrina Abyssinica*, *J. Nat. Prod.*, 2010, **73**, 598; (i) S. D. Chen, H. Gao, Q. C. Zhu, Y. Q. Wang, T. Li, Z. Q. Mu, H. L. Wu, T. Peng, X. S. Yao and A.-E. Houltunoids, Anti-Herpes Simplex Virus Active Flavonoids with Novel Skeletons from *Houttuynia cordata*, *Org. Lett.*, 2012, **14**, 1772; (j) G. Y. Luo, M. Zhou, Y. Liu, Q. Ye, J. Gu, T. F. Huang, G. L. Zhang and Y. G. Luo, 3-Formyl-2-Arylbenzofurans from the Aerial Parts of *Itea ilicifolia*, *Phytochem. Lett.*, 2014, **10**, 19.
- 9 (a) Z. Yang, H. B. Liu, C. M. Lee, H. M. Chang and H. N. C. Wong, Compounds from *Danshen*. Part 7. Regioselective Introduction of Carbon-3 Substituents to 5-Alkyl-7-methoxy-2-phenylbenzo[b]furans: Synthesis of a Novel Adenosine A_1 Receptor Ligand and its Derivatives, *J. Org. Chem.*, 1992, **57**, 7248; (b) R. Gastpar, M. Goldbrunner, D. Marko and E. von Angerer, Methoxy-Substituted 3-Formyl-2-phenylindoles Inhibit Tubulin Polymerization, *J. Med. Chem.*, 1998, **41**, 4965.
- 10 Y. Tang, C. Jiang, X. Zhang, C. Liu, J. Lin, Y. Wang, C. Du, X. Peng, W. Li, Y. Liu and M. Cheng, Collective Syntheses of 2-(3-Methylbenzofuran-2-yl)phenol-Derived Natural Products by a Cascade [3,3]-Sigmatropic Rearrangement/Aromatization Strategy, *J. Org. Chem.*, 2017, **82**, 11102.
- 11 Although 2,2-dimethyl-1,3-propandiol was used in MOM deprotection, EtOH also gave favorable results; J. H. Koh and M. R. Gagne, Pd^{II} - and Pt^{II} -Mediated Polycyclization Reactions of 1,5- and 1,6-Dienes: Evidence in Support of Carbocation Intermediates, *Angew. Chem., Int. Ed.*, 2004, **43**, 3459.
- 12 See reported reactions to go through diprotonated or dicationic intermediates under acidic conditions. (a) T. Suzuki, T. Ohwada and K. Shudo, Superacid-Catalyzed Electrocyclization of 1-Phenyl-2-propen-1-ones to 1-Indanones. Kinetic and Theoretical Studies of Electrocyclization of Oxonium-Carbenium Dications, *J. Am. Chem. Soc.*, 1997, **119**, 6774; (b) D. A. Klumpp, Y. Zhang, M. J. O'Connor, P. M. Esteves and L. S. de Almeida, Aza-Nazarov Reaction and the Role of Superelectrophiles, *Org. Lett.*, 2007, **9**, 3085; (c) N. Ghavtadze, R. Fröhlich, K. Bergander and E.-U. Würthwein, Superelectrophilic Intermediates in the Synthesis of Novel Indenole Derivatives via 1,5-Cyclization Reactions of 5-Aryl-1-azapenta-1,4-dien-3-ones, *Synthesis*, 2008, **21**, 3397; (d) H. Kurouchi, K. Kawamoto, H. Sugimoto, S. Nakamura, Y. Otani and T. Ohwada, Activation of Electrophilicity of Stable Y-Delocalized Carbamate Cations in Intramolecular Aromatic Substitution Reaction: Evidence for Formation of Diprotonated Carbamates Leading to Generation of Isocyanates, *J. Org. Chem.*, 2012, **77**, 9313; (e) Y.-K. Wu, T. Niu and F. G. West, Construction of α -Amido-indanones via Formal Allenamide Hydroacylation-Nazarov Cyclization, *Chem. Commun.*, 2012, **48**, 9186.
- 13 For reviews on $(\text{CF}_3)_2\text{CHOH}$; (a) T. Sugiishi, M. Matsugi, H. Hamamoto and H. Amii, Enhancement of Stereoselectivities in Asymmetric Synthesis Using Fluorinated Solvents, Auxiliaries, and Catalysts, *RSC Adv.*, 2015, **5**, 17269; (b) J. Wencel-Delord and F. A. Colobert, A Remarkable Solvent Effect of Fluorinated Alcohols on Transition Metal Catalysed C–H Functionalizations, *Org. Chem. Front.*, 2016, **3**, 394; (c) C. Yu, J. Sanjosé-Orduna, F. Patureau and M. Pérez-Temprano, Emerging Unconventional Organic Solvents for C–H Bond and Related Functionalization Reactions, *Chem. Soc. Rev.*, 2020, **49**, 1643.



- 14 (a) V. Pozhydaiev, M. Power, V. Gandon, J. Moran and D. Lebœuf, Exploiting Hexafluoroisopropanol (HFIP) in Lewis and Brønsted Acid-Catalyzed Reactions, *Chem. Commun.*, 2020, **56**, 11548; (b) M. A. Hussein, A. H. Dinh, V. T. Huynh and T. V. Nguyen, Synthesis of Tertiary Amines by Direct Brønsted Acid Catalyzed Reductive Amination, *Chem. Commun.*, 2020, **56**, 8691.
- 15 M. A. Marangoni, P. A. Moraes, A. F. Camargo, H. G. Bonacorso, M. A. P. Martins and N. Zanatta, Synthesis of a Novel 1,4-Dicarbonyl Scaffold – Ethyl 3-Formyl-4,5-dihydro-furan-2-carboxylate- and Its Application to the Synthesis of Pyridazines, *Synthesis*, 2020, **52**, 2528.
- 16 The related conversions are known to require heating under basic conditions; (a) Z. V. Chirkova, M. V. Kabanova, D. V. Luferenko, S. I. Filimonov and I. G. Abramov, Formation of 4-Hydroxy-5-[aryl(alkyl)-1H-pyrazol-4-yl] benzene-1,2-dicarbo-nitriles in Reactions of Benzofurans with Hydrazines, *Russ. J. Org. Chem.*, 2015, **51**, 644; (b) K. Srinivas, R. Sharma and C. V. Ramana, Interrupting Base-Mediated Benzofuran Ring Transformation with Michael Acceptors, *J. Org. Chem.*, 2017, **82**, 9816; (c) I. Khelifi, G. Zhao, N. Ghermani, O. Provot and M. Alami, Unexpected Oxidative Ring Opening of Electron-Rich 3-Aminobenzofurans into α -Ketoimines Derivatives, *J. Org. Chem.*, 2019, **84**, 1725.

