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ULTRASOUND PROMOTED EFFICIENT CONSTRUCTION OF POLYCYCLIC-FUSED PYRAZOLO[4,3-*c*]PYRIDINES VIA DOMINO REACTION

Ting Zhou,[1] Dao-Lin Wang,[1]* Jiao Xu,[2,3]* Liang Yan,[1] and Wei Ma[3]

[1]College of Chemistry and Chemical Engineering, Bohai University, Jinzhou, China, [2]Heilongjiang University of Chinese Medicine, Harbin, China, [3]Northeast Forestry University, Harbin, China. *Corresponding authors E-mail: wangdaolin@sina.com; xujiao2007@sina.com

Abstract – Ultrasonic-accelerated rapid protocol for the synthesis of polycyclic-fused pyrazolo[4,3-*c*]pyridines *via* S_N2/Thorpe-Ziegler/Thorpe-Guareschi domino reactions of 4-acetyl-5-bromomethyl-1-phenyl-1*H*-pyrazole with salicylonitriles (2-mercaptobenzonitrile or 3-cyanopyridine-2(1*H*)-thiones). Ultrasound-based methodology performed better than the conventional process in rates and yields.

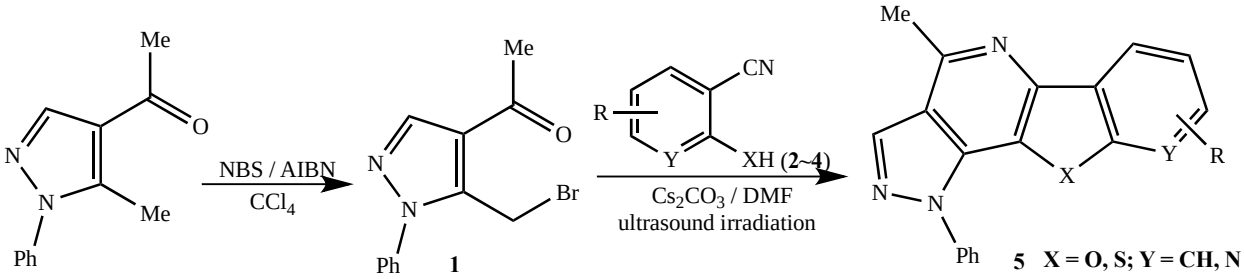
Pyrazole derivatives are an important class of heterocyclic compound for being key substructures in a variety of compounds with important biological properties.[1] They are known to possess a wide spectrum of activities such as antimicrobial,[2] antiinflammatory,[3] antidepressant,[4] antiviral,[5] and antitumour activities.[6] Many heterocyclic compounds containing the pyrazole ring display a broad spectrum of pharmacological and biological activities.[7,9] Moreover, the pyrazole nucleus represent the core unit in a variety of drugs such as celecobix (Celebrex)[8] and sildenafil (Viagra).[9]

Furthermore, the pyrazolopyridine moiety, which is a well-known nitrogen-containing fused-heterocycle, is a common and important feature of a variety of medicinal agents because of their wide range of biological and pharmaceutical properties such as antibacterial,[10] antimicrobial,[11] and oncogenic Ras inhibiting activities.[12] Furthermore, these compounds can be used as promising luminescent materials[13] and a fluorescent sensor.[14] Owing to the attractive pharmacological properties of pyrazoles, new methodologies for the design of different pyrazoles have attracted the attention of the researchers.

In recent years, the application of ultrasound irradiation in organic reactions has been rapidly increasing. A large number of organic reactions can be carried out in a higher yield, shorter reaction time and milder

conditions under sonication.[15]

Recently, our group is actively engaged in the development of cascade synthesis of heterocycles and has developed a number of domino reactions to synthesize different heterocycles.[16] Herein, we report the polycyclic-fused pyrazolo[4,3-*c*]pyridines **5** preparation *via* S_N2/Thorpe-Ziegler/Thorpe-Guareschi domino reaction[17] from 4-acetyl-5-bromomethyl-1-phenyl-1*H*-pyrazole with salicylonitriles (2-mercapto-benzonitrile or 3-cyanopyridine-2(1*H*)-thiones) under ultrasound irradiation (Scheme 1).



Scheme 1. Synthesis of polycyclic-fused pyrazolo[4,3-*c*]pyridines

In order to evaluate the potential of the synthesis procedure and to optimize the reaction conditions, the reaction of 4-acetyl-5-bromomethyl-1-phenyl-1*H*-pyrazole (**1**) and salicylonitrile (**2**) as a model was investigated. The results are summarized in **Table 1**.

Table 1. Optimization of reaction conditions on the synthesis of **5a**[a]

Entry	Base	Solvent	Temp (°C)	Conventional		Sonication	
				Time (h)[b]	Yield (%)[c]	Time (h)[b]	Yield (%)[c]
1	K_2CO_3	DMF	100	9	67	4	80
2	Cs_2CO_3	DMF	100	7	75	3	86
3	*t*-BuOK	DMF	100	8	70	4	82
4	Cs_2CO_3	DMSO	100	7	64	5	78
5	Cs_2CO_3	NMP	100	7	72	3	83
6	Cs_2CO_3	DMF	90	9	74	4	80
7	Cs_2CO_3	DMF	110	6	72	3	85

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.0 equiv), base (2.0 equiv), solvent (20 mL).
[b] Reaction progress monitored by TLC.
[c] Isolated yield.

As indicated in **Table 1**, several bases (K_2CO_3, Cs_2CO_3 and *t*-BuOK) were screened, and Cs_2CO_3 was relatively efficient with 86% yield of **5a** under ultrasound irradiation (entry 2). Solvent was investigated

and DMF was found to be more effective than DMSO and NMP (entries 4 and 5). Further increase (110 °C) or decrease (90 °C) of reaction temperature did not push this domino reaction forward (entries 6 and 7).

To explore the scope and limitation of this reaction, we have extended the reaction of 4-acetyl-5-bromomethyl-1-phenyl-1*H*-pyrazole (**1**) with a range of salicylonitriles (**2**) (2-mercaptobenzonitrile (**3**) or 3-cyanopyridine-2(1*H*)-thiones (**4**)) under optimum conditions (DMF/100 °C/Cs_2CO_3/ultrasound), furnishing the respective fused pyrazolo[4,3-*c*]pyridines (**5a–h**), and obtained results are summarized in **Table 2**.

Table 2. Synthesis of fused pyrazolo[4,3-*c*]pyridines **5**

Entry	Products	R	X	Y	Conventional		Sonication	
					Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
1	**5a**	H	O	C	7	75	3	86
2	**5b**	7-Me	O	C	6	76	3	83
3	**5c**	7-OMe	O	C	6	70	4	82
4	**5d**	H	S	C	5	78	2	91
5	**5e**	7-Cl	S	N	9	65	2	83
6	**5f**	H	S	N	7	82	2	94
7	**5g**	6-Me	S	N	8	71	3	87
8	**5h**	8-Me	S	N	8	75	3	88

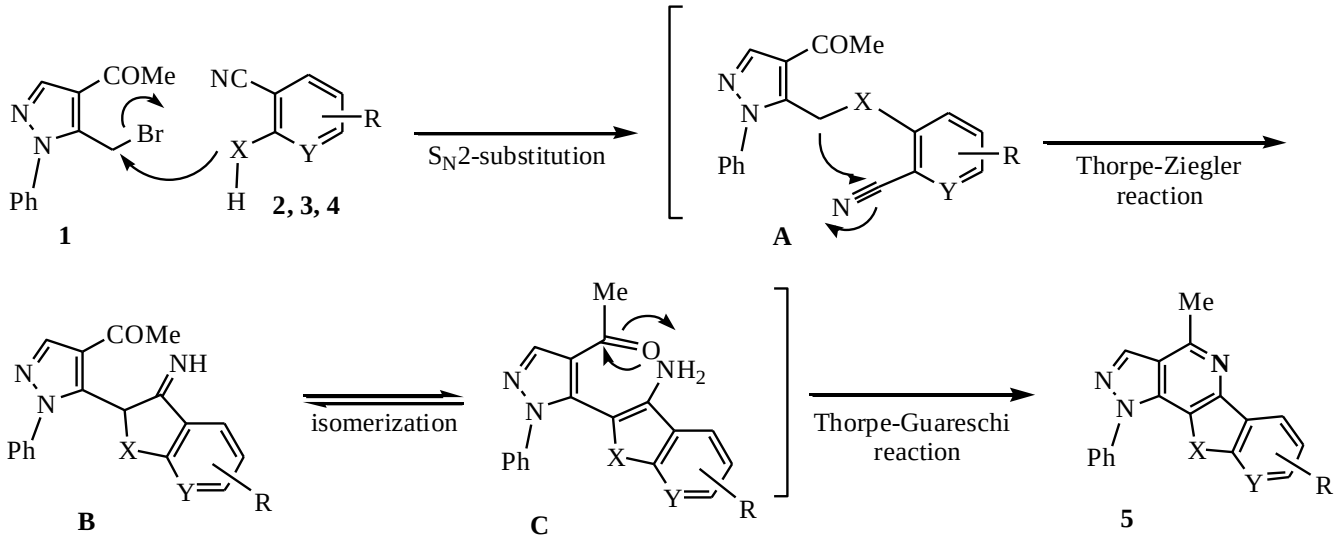
[a] Isolated yields.

In order to verify the effect of ultrasound irradiation, all the reactions were carried out under the same conditions in absence of ultrasound irradiation (**Table 2**). The desired products were produced in much longer reaction time (5–9 h) and relatively lower yields (65–82%), while under ultrasonic irradiation the products were obtained in 2–4 h with the yields of 82–94%. The method to obtain the desired products under ultrasonic irradiation offers several significant advantages including faster reaction rates and higher yields. Thus, ultrasonic irradiation was found to have beneficial effect on the synthesis of polycyclic-fused pyrazolo[4,3-*c*]pyridine derivatives.

To the best of our knowledge, this new procedure provides the first example of an efficient and ultrasound promoted approach for the synthesis of furo- and thieno-fused pyrazolo[4,3-*c*]pyridine derivatives. This method is the most simple and convenient and would be applicable for the synthesis of different types of tetracyclic system heterocycles containing pyrazole, pryidine and benzofuran or

benzothiophene unit with high regioselectivity. The structures of all the synthesized compounds were established by IR, NMR spectroscopy and elemental analysis.

The proposed mechanism of the process is summarized in Scheme 2. The present synthetic sequence was initiated by an alkylation of 4-acetyl-5-bromomethyl-1-phenyl-1*H*-pyrazole **1** with salicylonitriles (**2**) (2-mercaptobenzonitrile (**3**) or cyanopyridine-2(1*H*)-thiones (**4**)) giving to the ethers **A**. An intramolecular carbanion addition across the nitrile was brought about by ethers **A** *via* Thorpe-Ziegler reaction, and isomerization, resulting in the formation of amines **C**. Next, this then undergoes Thorpe-Guareschi reaction to yield the fused pyrazolo[4,3-*c*]pyridines **5**.



Scheme 2. Proposed mechanism for the synthesis of compounds **5**

In conclusion, it has been successfully developed that S_N2/Thorpe-Ziegler/Thorpe-Guareschi domino reaction under ultrasonic condition, and a series of novel furo- and thieno-fused pyrazolo[4,3-*c*]pyridines were obtained. This method has the advantages of ultrasonic irradiation of convenient operation, mild reaction conditions, short reaction time and high efficiency.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H, and N analyses were performed by a HP-MOD 1106 microanalyzer. Ultrasonication was performed in a KQ-250E medical ultrasound cleaner with a frequency of 25 KHz and an output power of 250 W. The preparation of 4-acetyl-5-methyl-1-phenyl-1*H*-pyrazole was according to the literature procedure.[18] All other chemicals used in this study were commercially available.

Synthesis of 4-acetyl-5-bromomethyl-1-phenyl-1*H*-pyrazole (1). To a solution of 4-acetyl-5-methyl-1-phenyl-1*H*-pyrazole (2.00 g, 10.0 mmol) in carbon tetrachloride (200 mL) containing azodiisobutyronitrile (AIBN) (150 mg, 0.91 mmol) was added *N*-bromosuccinimide (NBS) (1.78 g, 10.0 mmol) and refluxed for 4 h. After the reaction mixture was cooled, it was diluted with water (50 mL). The extract was dried over sodium sulfate and evaporated in vacuo to leave a residue which was recrystallized from propan-2-ol to give **1** (2.56 g, 92%). Red needles. Mp 152-154 ºC; IR (KBr, cm^{-1}): *v* 1654 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.68 (s, 3H), 3.43 (s, 2H), 7.59-7.67 (m, 3H), 7.73-7.76 (m, 2H), 9.03 (s, 1H). *Anal*. Calcd for $C_{12}H_{11}BrN_2O$: C 51.63, H 3.97, N 10.04. Found: C 51.69, H 4.08, N 10.12.

General procedure for the synthesis of pyrazolo[4,3-*c*]pyridine under conventional conditions. To a solution of 4-acetyl-5-bromomethyl-1-phenyl-1*H*-pyrazole (**1**) (279 mg, 1.0 mmol) in DMF (20 mL) was added salicylonitrile (**2**) (2-mercaptobenzonitrile (**3**) or 3-cyanopyridine-2(1*H*)-thiones (**4**)) (1.0 mmol) and cesium carbonate (651 mg, 2.0 mmol). The mixture was heated at 100 °C for appropriate time as shown in **Table 2**. After the reaction mixture was then cooled to rt, and then diluted with water (20 mL). The solid was filtered and recrystallized from HOAc to afford the corresponding products **5a-h**.

General procedure for the synthesis of pyrazolo[4,3-*c*]pyridine under ultrasound irradiation. To a solution of 4-acetyl-5-bromomethyl-1-phenyl-1*H*-pyrazole (**1**) (279 mg, 1.0 mmol) in DMF (20 mL) was added salicylonitrile (**2**) (2-mercaptobenzonitrile (**3**) or 3-cyanopyridine-2(1*H*)-thiones (**4**)) (1.0 mmol) and cesium carbonate (651 mg, 2.0 mmol). The reaction mixture was irradiated under sonication at 100 °C for appropriate time as shown in **Table 2**. After the reaction mixture was then cooled to rt, and then diluted with water (20 mL). The solid was filtered and recrystallized from HOAc to afford the corresponding products **5a-h**.

4-Methyl-1-phenyl-1*H*-benzofuro[3,2-*b*]pyrazolo[5,4-*d*]pyridine (5a): Red needles. Mp > 300 ºC; ^{1}H NMR (CF_3CO_2D): δ 3.30 (s, 3H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.66-7.68 (m, 4H), 7.72-7.80 (m, 3H), 8.17 (d, *J* = 8.0 Hz, 1H), 9.12 (s, 1H). ^{13}C NMR (CF_3CO_2D): δ 16.3, 117.2, 117.3, 121.3, 123.1, 126.0, 126.4, 126.7, 130.0, 130.7, 131.8, 134.8, 135.2, 138.2, 138.7, 139.8, 151. 8. *Anal*. Calcd for $C_{19}H_{13}N_3O$: C 76.24, H 4.38, N 14.04. Found: C 76.31, H 4.40, N 14.07.

4,7-Dimethyl-1-phenyl-1*H*-benzofuro[3,2-*b*]pyrazolo[5,4-*d*]pyridine (5b): Red needles. Mp > 300 ºC; ^{1}H NMR (CF_3CO_2D): δ 2.46 (s, 3H), 3.32 (s, 3H), 7.50 (s, 1H), 7.63-7.65 (m, 3H), 7.70-7.81 (m, 3H), 8.15 (d, *J* = 8.0 Hz, 1H), 9.15 (s, 1H). ^{13}C NMR (CF_3CO_2D): δ 16.6, 23.4, 116.2, 117.0, 121.2, 123.1, 126.1, 126.3, 126.7, 130.3, 130.7, 131.5, 134.2, 135.0, 138.5, 138.9, 139.7, 151.5. *Anal.* Calcd for $C_{20}H_{15}N_3O$: C 76.66, H 4.82, N 13.41. Found: C 76.72, H 4.93, N 13.45.

4-Methyl-7-methoxy-1-phenyl-1*H*-benzofuro[3,2-*b*]pyrazolo[5,4-*d*]pyridine (5c): Red needles. Mp > 300 ºC; ^{1}H NMR (CF_3CO_2D): δ 3.36 (s, 3H), 3.98 (s, 3H), 7.28 (s, 1H), 7.60-7.66 (m, 3H), 7.76-7.84 (m, 3H), 8.24 (d, *J* = 8.0 Hz, 1H), 9.19 (s, 1H). ^{13}C NMR (CF_3CO_2D): δ 23.2, 54.7, 115.4, 116.5, 121.9, 123.8,

126.0, 126.3, 126.6, 130.1, 130.9, 131.4, 134.6, 135.7, 138.5, 138.3, 139.2, 153.2. *Anal.* Calcd for $C_{20}H_{15}N_3O_2$: C 72.94, H 4.95, N 12.76. Found: C 73.02, H 4.97, N 12.80.

7-Chloro-4-methyl-1-phenyl-1*H*-benzofuro[3,2-*b*]pyrazolo[5,4-*d*]pyridine (5d): Red needles. Mp > 300 °C; ^{1}H NMR (CF_3CO_2D): δ 3.36 (s, 3H, CH_3), 7.28 (s, 1H), 7.62-7.68 (m, 3H), 7.74-7.82 (m, 3H), 8.31 (d, J = 8.0 Hz, 1H), 9.21 (s, 1H). ^{13}C NMR (CF_3CO_2D): δ 23.7, 116.1, 116.9, 120.8, 122.7, 125.7, 126.1, 126.8, 130.4, 130.8, 131.4, 134.8, 135.5, 138.5, 138.7, 139.4, 153.6. *Anal.* Calcd for $C_{19}H_{12}ClN_3O$: C 68.37, H 3.62, N 12.59. Found: C 68.42, H 3.67, N 12.63.

4-Methyl-1-phenyl-1*H*-benzothieno[3,2-*b*]pyrazolo[5,4-*d*]pyridine (5e): Red needles. Mp > 300 °C; ^{1}H NMR (CF_3CO_2D): δ 3.32 (s, 3H), 7.62-7.71 (m, 6H), 7.74-7.76 (m, 1H), 7.88 (d, J = 7.6 Hz, 1H), 8.44 (d, J = 7.6 Hz, 1H), 9.07 (s, 1H). ^{13}C NMR (CF_3CO_2D): δ 16.8, 117.1, 119.2, 123.4, 125.7, 127.6, 130.1, 132.7, 133.4, 134.1, 138.7, 139.7, 140.9, 144.2, 150.9, 156.5. *Anal.* Calcd for $C_{19}H_{13}N_3S$: C 72.36, H 4.15, N 13.32. Found: C 72.42, H 4.18, N 13.39.

4-Methyl-1-phenyl-1*H*-pyrido[2',3':5,4]thieno[3,2-*b*]pyrazolo[5,4-*d*]pyridine (5f): Red needles. Mp > 300 °C; ^{1}H NMR (CF_3CO_2D): δ 3.36 (s, 3H), 7.58-7.68 (m, 2H), 7.70-7.72 (m, 2H), 7.77 (t, J = 7.6 Hz, 1H), 8.22-8.25 (m, 1H), 9.13-9.14 (m, 1H), 9.17 (s, 1H), 9.71 (d, J = 8.0 Hz, 1H). ^{13}C NMR (CF_3CO_2D): δ 20.2, 115.2, 119.2, 126.7, 127.4, 128.2, 128.9, 129.2, 130.4, 131.1, 135.1, 140.0, 140.9, 150.7, 157.3, 158.6. *Anal.* Calcd for $C_{18}H_{12}N_4S$: C 68.33, H 3.82, N 17.71. Found: C 68.40, H 3.85, N 17.75.

4,8-Dimethyl-1-phenyl-1*H*-pyrido[2',3':5,4]thieno[3,2-*b*]pyrazolo[5,4-*d*]pyridine (5g): Red needles. Mp > 300 °C; ^{1}H NMR (CF_3CO_2D): δ 2.91 (s, 3H), 3.28 (s, 3H), 7.51-7.71 (m, 5H), 7.93-7.94 (m, 1H), 9.08 (m, 1H), 9.41-9.45 (m, 1H). ^{13}C NMR (CF_3CO_2D): δ 16.8, 19.4, 116.1, 119.0, 124.6, 124.9, 125.7, 130.5, 132.6, 133.6, 134.2, 138.8, 139.7, 140.0, 150.3, 156.2, 158.9. *Anal.* Calcd for $C_{19}H_{14}N_4S$: C 69.07, H 4.27, N 16.96. Found: C 69.11, H 4.32, N 17.04.

4,6,8-Trimethyl-1-phenyl-1*H*-pyrido[2',3':5,4]thieno[3,2-*b*]pyrazolo[5,4-*d*]pyridine (5h): Red needles. Mp > 300 °C; ^{1}H NMR (CF_3CO_2D): δ 2.80 (s, 3H), 3.21 (s, 3H), 3.29 (s, 3H), 7.46-7.68 (m, 6H), 9.03-9.06 (m, 1H). ^{13}C NMR (CF_3CO_2D): δ 17.8, 18.9, 20.4, 110.0, 116.1, 118.7, 123.9, 125.9, 126.3, 130.5, 132.7, 134.1, 138.7, 139.8, 150.2, 156.2, 156.6, 157.4. *Anal.* Calcd for $C_{20}H_{16}N_4S$: C 69.74, H 4.68, N 16.27. Found: C 69.79, H 4.72, N 16.32.

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REFERENCES

1. G. Szabo, J. Fischer, A. Kis-Varga, and K. Gyires, *J. Med. Chem.*, 2008, **51**, 142.

2. (a) M. Li and B. X. Zhao, *Eur. J. Med. Chem.*, 2014, **85**, 311; (b) S. Ningaiah, U. K. Bhadraiah, S. D. Doddaramappa, S. Keshavamurthy, and C. Javarasetty, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 245.
3. A. K. Tewari, V. P. Singh, P. Yadav, G. Gupta, A. Singh, R. K. Goel, P. Shinde, and G. C. Mohan, *Bioorg. Chem.*, 2014, **56**, 8.
4. M. Abdel-Aziz, A. G. Abuo-RahmaEI-Din, and A. A. Hassan, *Eur. J. Med. Chem.*, 2009, **44**, 3480.
5. A. I. Hashem, A. S. A. Youssef, K. A. Kandeel, and W. S. I. Abou-Elmagd, *Eur. J. Med. Chem.*, 2007, **42**, 934.
6. P. Khloya, G. Celik, S. Ram, V. Vullo, C. T. Supuran, and P. K. Sharma, *Eur. J. Med. Chem.*, 2014, **76**, 284.
7. S. K. Singh, P. G. Reddy, K. S. Rao, B. B. Lohray, P. Misra, S. A. Rajjak, Y. K. Rao, and A. Venkatewarlu, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 499.
8. T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, and P. C. Isakson, *J. Med. Chem.*, 1997, **40**, 1347.
9. N. K. Terrett, A. S. Bell, D. Brown, and P. Ellis, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1819.
10. S. F. Thakor, D. M. Patel, M. P. Patel, and R. G. Patel, *Saudi. Pharma. J.*, 2007, **15**, 48.
11. O. A. El-Sayed and H. Y. Aboul-Enein, *Arch. Pharm.*, 2001, **334**, 117.
12. R. Wolin, D. Wang, J. Kelly, A. Afonso, L. James, P. Kirschmeier, and A. T. McPhail, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 195.
13. E. Gondek, I. V. Kityk, J. Sanetra, P. Szlachcic, P. Armatys, A. Wisla, and A. Danel, *Optics Laser Tech.*, 2006, **38**, 487.
14. P. Cywinski, B. Wandelt, and A. Danel, *Adsorpt. Sci. Technol.*, 2004, **22**, 719.
15. (a) B. Banerjee, *Ultrason. Sonochem.*, 2017, **35**, 15; (b) R. Cella and H. A. Stefani, *Tetrahedron*, 2009, **65**, 2619.
16. (a) D.-L. Wang, J. Ma, X.-C. Shi, and J.-Y. Wu, *Heterocycles*, 2016, **92**, 133; (b) D.-L. Wang, T. Zhou, J.-J. Xing, J.-H. Qiang, and L. Liu, *Heterocycles*, 2016, **92**, 733; (c) D.-L. Wang, J.-Y. Wu, D. Wu, and Y.-Y. Wang, *Chin. Chem. Lett.*, 2014, **25**, 1555.
17. (a) L. F. Tietze, G. Brasche, and K. M. Gericke, *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006, 617; (b) A. M. Shestopalov, L. A. Rodinovskaya, and A. A. Shestopalov, *J. Comb. Chem.*, 2010, **12**, 9.
18. H. Alinezhad, M. Tajbakhsh, and M. Zare, *Monatsh. Chem.*, 2012, **143**, 947.