RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2022, **12**, 34634

Synthesis of fully functionalised spiropyran pyrazolone skeletons *via* a formal [4 + 2] cascade process using β-nitro-styrene-derived MBH-alcohols†

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Received 27th September 2022
Accepted 12th November 2022

DOI: 10.1039/d2ra06076k

rsc.li/rsc-advances

An efficient protocol was established to construct spiro pyrazolone tetrahydropyran scaffolds at ambient temperature under metal-free conditions. The reaction proceeded *via* formal [4 + 2] cyclisation of *trans*-β-nitro-styrene-derived Morita–Baylis–Hillman (MBH) alcohol with α-arylidene pyrazolone. The reaction followed an oxa-Michael/Michael cascade pathway, resulting in the formation of new C–C and C–O bonds. Organocatalytic synthesis of spiropyrazolones using quinine-derived catalyst resulted in 94% enantiomeric excess (ee) and excellent (>20 : 1) diastereoselectivity.

The nitrogen-containing pyrazolone compounds are highly efficient and amenable to their activity as antimicrobials, antitumor agents, and type 4 inhibitors of phosphodiesterase, and thereby play a crucial role in pharmaceutical and medicinal chemistry (Fig. 1).[1] The synthesis of skeletons possessing spirocyclohexane pyrazolones,[2] spiropyrazolone tetrahydroquinolines,[3] spirobenzofuran pyrazoloedione,[4] spiropyroloidinepyrazolones,[5] spiro tetrahydrofuran pyrazolones,[6] spiropyrazolone epoxide,[7a] spiro oxindole-fused spiropyrazolones,[7b] spirooxindole pyrrolidine pyrazolone,[8] spiropyrazolonecyclohexene carbaldehydes,[9] spiropyrazolonecyclohexanone,[10] and fused pyrazolones such as dihydropyranopyrazoles[11] and tetrahydropyranopyrazoles[12] has received considerable interest in recent years. Arylidene pyrazolone has attracted considerable attention due to its unique 1,2-ambiphilic nature for the construction of elegant building blocks such as spirocycles,[13] dispirocycles[14] and fused heterocycles.[15a–c] Spiropyrazolones have been synthesized from the reaction of α-arylidene pyrazolone with various substrates, but the reaction using MBH adducts are scarce.[15d] To the best of our knowledge, there has been to date only one report on the synthesis of spiropyrazolone tetrahydropyran derivatives using alkylidene trimethylene carbonate,[16] and no report on the synthesis of functionalized spiropyrazolones using MBH-alcohol with 5 contiguous stereocenters. Of the MBH adducts, β-nitro-styrene-derived MBH adducts were previously used by various research groups for the construction of spiropyrazolone skeletons (Scheme 1).

Enders and his team carried out a sequential organo- and silver catalysis for the synthesis of spiropyrazolones using alkyne-tethered nitroalkenes[17] (eqn (a), Scheme 1). Miao *et al.* reported the synthesis of spirochromane 3,3 pyrazoles using 2-nitro vinyl phenols[18] (eqn (b), Scheme 1). Chen and co-workers constructed spiranopyrazoles[19] using 5-nito-6-phenyl-hex-5-en-2-one (eqn (c), Scheme 1). On the other hand, the utility of nitro-styrene-derived MBH alcohols as 1,4-*bis*-ambiphiles (α-C, δ-O) has been less extensively investigated.[20] In continuation of our efforts towards the synthesis of various spirocyclic systems,[21] herein we report the synthesis of spiropyrazolone tetrahydropyran scaffolds using β-nitro-styrene-derived MBH alcohols, resulting in the formation of the desired products with

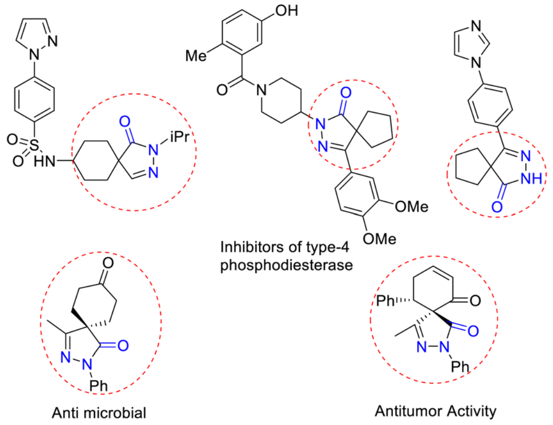

Fig. 1 Biologically active spiropyrazolone skeletons.

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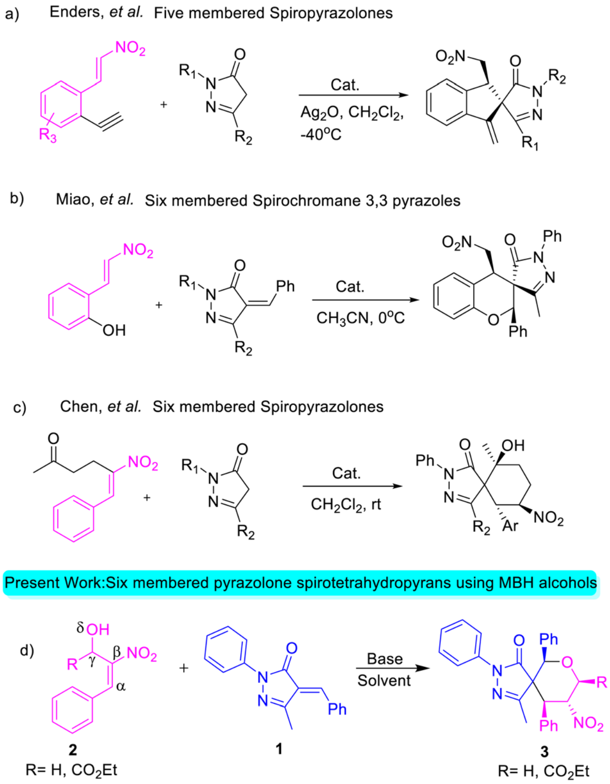
† Electronic supplementary information (ESI) available. CCDC 2215596. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2ra06076k

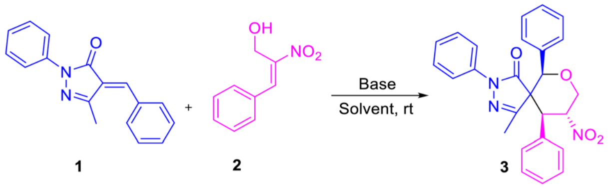


Scheme 1 Annulation reactions using β-nitro-styrene-derived adducts.

4 to 5 contiguous chiral centers through [4 + 2] annulation (eqn (d), Scheme 1).

Initially, we carried out an optimization of conditions for the construction of spiro pyrazolone tetrahydropyran scaffolds using various types of solvents and bases at room temperature. Treatment of unsaturated arylidene pyrazolone and nitro-styrene-derived primary MBH alcohol using DABCO in the presence of acetonitrile (CH_3CN) furnished the desired product in 16% yield (entry 1, Table 1). Performing the reaction instead in a polar solvent, *e.g.*, THF, did not improve the yield (entry 2, Table 1). And performing the reaction instead in a chlorinated solvent, *e.g.*, $CHCl_3$ or DCM, also did not considerably enhance the yield of product **3a** (entries 3 and 4, Table 1). An increase in yield was observed by shifting to an inorganic base, *i.e.*, Cs_2CO_3, which together with using CH_2Cl_2 as the solvent gave the product **3a** in 60% yield (entry 5, Table 1); and here, use of the

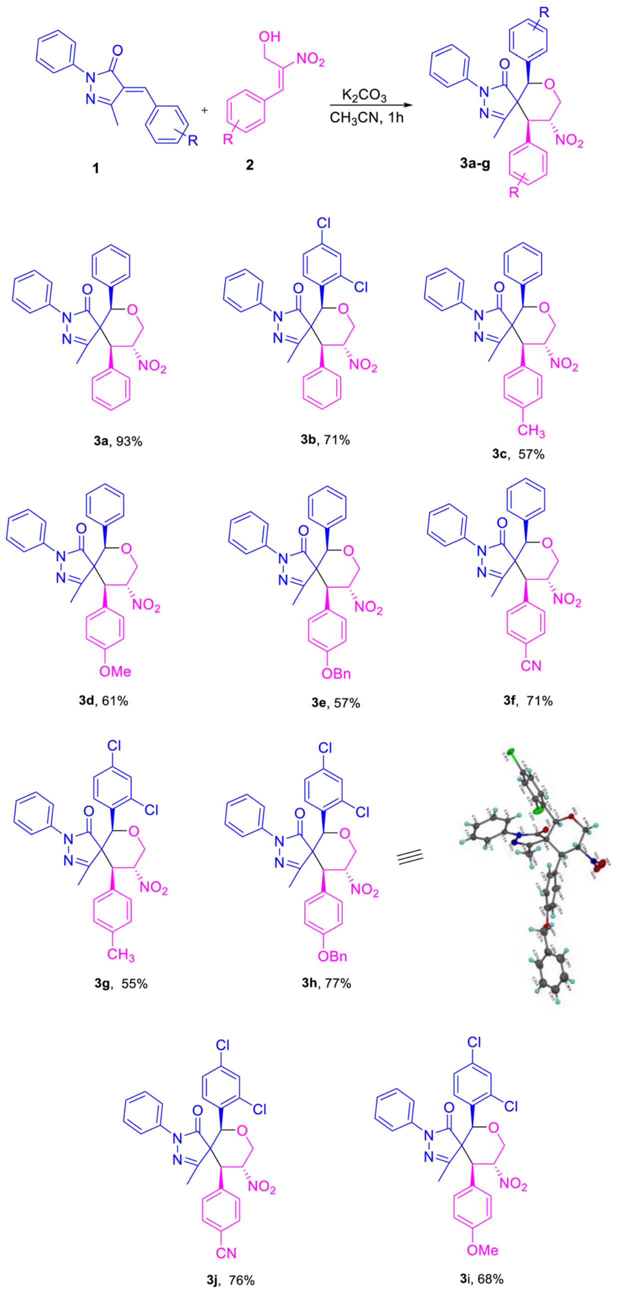
Table 1 Optimization of reaction conditions for the synthesis of spiropyran pyrazolone using β-nitro-styrene-derived 1° MBH alcohol[a]



Entry	Base	Solvent	Time (h)	Yield (%)	dr[b]
1	DABCO	CH_3CN	8	16	n.d
2	DABCO	THF	7	22	n.d
3	DABCO	$CHCl_3$	7	27	>20 : 1
4	DABCO	DCM	7	25	n.d
5	Cs_2CO_3	CH_2Cl_2	1	60	> 20 : 1
6	Cs_2CO_3	CH_3CN	1	66	>20 : 1
7	$\mathbf{K_2CO_3}$	$\mathbf{CH_3CN}$	**1**	**93**	**>20 : 1**
8[c]	K_2CO_3	CH_3CN	1	76	>20 : 1

[a] Unless otherwise noted, reactions were carried out with (0.19 mmol of) **1** with (0.28 mmol of) **2** using 0.47 mmol of base in 1.5 ml of CH_3CN solvent. [b] Determined from a ^{1}H-NMR analysis of a crude reaction mixture. [c] Reaction carried out at 60 °C.

Table 2 Substrate scope for the synthesis of spiropyran pyrazolone



polar aprotic solvent CH_3CN instead of CH_2Cl_2 increased the yield to 66% (entry 6, Table 1). The best reaction conditions were obtained when using K_2CO_3 as an inorganic base in CH_3CN to obtain product **3a** in 93% yield (entry 7, Table 1). A decrease in the yield for product formation was observed when heating the reaction mixture at 60 °C (entry 8, Table 1).

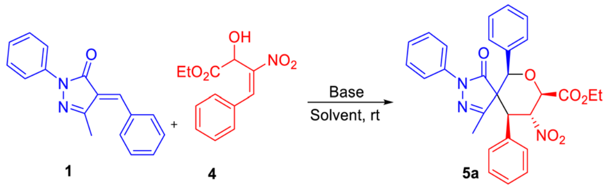
Based on the best optimized conditions, we studied the scope of different substituents at the aryl ring of pyrazolone **1** as well as primary MBH alcohol **2**. The 2,4-dichloro-substituted arylidene pyrazolone **1b** gave the desired product **3b** in 71% yield (Table 2). Use of the electron-donating group $-CH_3$ at the *para* position of the MBH alcohol furnished the corresponding product **3c** in 57% yield. Electron-rich donating groups –OMe and –OBn gave **3d–e** in 61 and 57% yields, respectively. An electron-withdrawing group at the *para* position also gave a good yield for product **3f**. We examined the yield and functional group tolerance by changing the substituents at arylidene pyrazolones and MBH alcohols; here, products **3g–j** were obtained in moderate to good yields.

We next focused on building fully substituted spiro pyrazolone tetrahydropyrans scaffolds **5a–c** using β-nitro-styrene-derived secondary (2°)-MBH alcohols with arylidene pyrazolones. With the best optimized set of conditions obtained previously, we carried out the construction of fully substituted spiropyran pyrazolone using K_2CO_3 in CH_3CN to give **5a** in 67% yield (entry 1, Table 3). The chlorinated solvents CH_2Cl_2, $CHCl_3$, and CCl_4 gave **5a** in only 41–56% yields (entries 2–4, Table 3). And a further decline in yield was observed when using instead THF as solvent (entry 5, Table 3). We found that Cs_2CO_3 in the presence of $CHCl_3$ was the best base–solvent combination for the formation of product **5a**, with a 78% yield and good diastereoselectivity (entry 6, Table 3).

Use of the electron-donating groups methyl and methoxy at the *para* position of the MBH alcohol resulted in 56–60% yields of product, *i.e.*, of **5c** and **5b** (Table 4). Furthermore, all the compounds **3a–j** and **5a–c** were confirmed from the results of IR, ^1H, ^{13}C NMR, HRMS, and NOESY analyses. The compound **3h** was further confirmed using single-crystal XRD (Table 2).[22]

We further pursued our studies towards asymmetric synthesis of spiropyrazolones **3a** using various chiral catalysts (**I–IV**). We observed a poor enantiomeric excess for the product formation in the presence of cinchona catalyst **I** (entry 1, Table 5). Using NOBIN-based catalysts **II** and **III** resulted each in a 10% enantiomeric excess (entries 3–4, Table 5). Interestingly, we obtained an excellent enantiomeric excess (94% ee) with high diastereoselectivity (>20 : 1) when using the thiourea-based hydrogen bonding catalyst **IV** (entry 4, Table 5; see ESI† for information on the transition state).

Table 3 Optimization for the synthesis of fully substituted spiropyran pyrazolones using β-nitro-styrene-derived 2° MBH alcohol[a]



Entry	Base	Solvent	Time (h)	Yield	dr[b]
1	K_2CO_3	CH_3CN	1	67	>20 : 1
2	K_2CO_3	CH_2Cl_2	1	56	n.d
3	K_2CO_3	$CHCl_3$	1	47	>20 : 1
4	K_2CO_3	CCl_4	1	41	>10 : 1
5	K_2CO_3	THF	1	36	n.d
6	**Cs_2CO_3**	**$CHCl_3$**	**1**	**78**	**>20 : 1**

[a] Unless otherwise noted, reactions were carried out with (0.19 mmol of) **1** with (0.28 mmol of) **4** using 0.47 mmol% of base in 1.5 ml of $CHCl_3$ solvent. [b] Diastereomeric ratio was determined from ^1H-NMR analysis of a crude reaction mixture.

Table 4 Substrate scope for the synthesis of fully substituted spiropyran pyrazolones

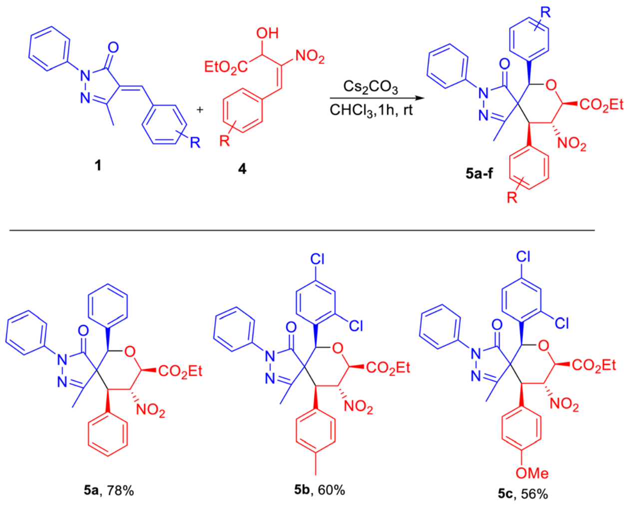
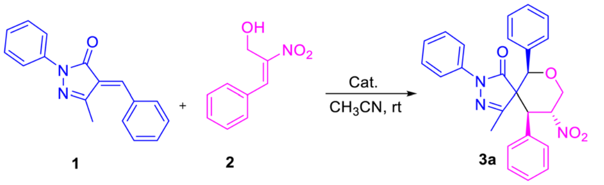
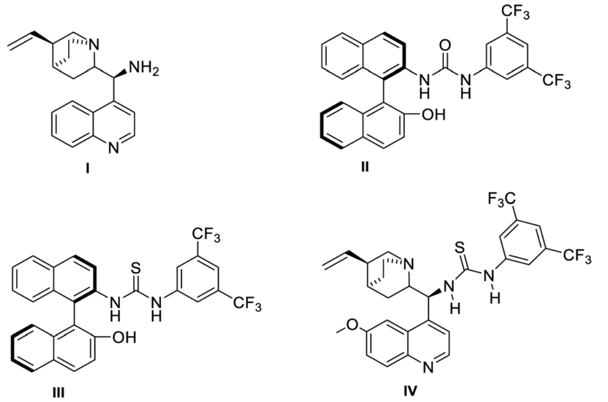


Table 5 Asymmetric version of spiro pyrazolone tetrahydropyran **3a**[a]



Entry	Catalyst	Time (h)	Yield (%)	ee[b] (%)	dr[c]
1	**I**	1	35	50	>20 : 1
2	**II**	1	>10	17	>20 : 1
3	**III**	1	>15	11	>20 : 1
4	**IV**	**1**	**61**	**94**	**>20 : 1**

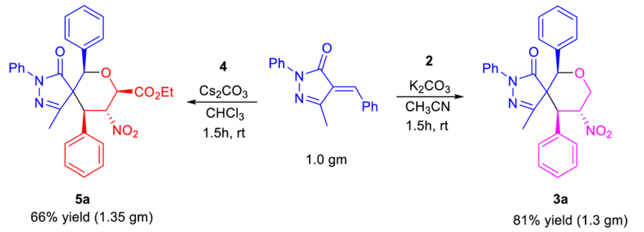
[a] All the reactions were carried out with (0.19 mmol of) **1**, (0.11 mmol of) **2** and 10 mol% of catalyst in 1 ml of CH_3CN solvent. [b] Enantiomeric excess determined from HPLC analysis. [c] Diastereomeric ratio was determined from ^1H-NMR analysis of a crude reaction mixture.



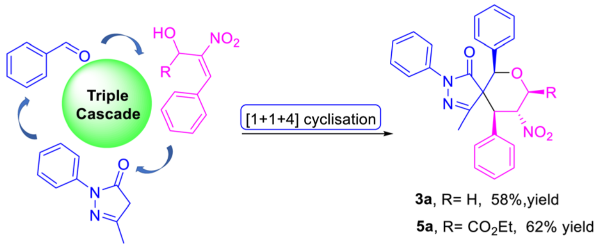
To further demonstrate the practical and scalable utility of our protocol, we carried out gram scale preparation of spiro pyrazolone tetrahydropyrans **3a** and **5a**, and achieved yields of 81% and 66% (Scheme 2).

We investigated the feasibility of carrying out a triple-cascade reaction for the construction of spiro pyrazolone tetrahydropyrans **3a** and **5a** *via* the Knoevenagel/oxa-Michael/Michael process. To our delight, the reaction was amenable to a one-pot [1 + 1 + 4] formal cyclization to give the products **3a** and **5a** in 58% and 62% yields (Scheme 3).

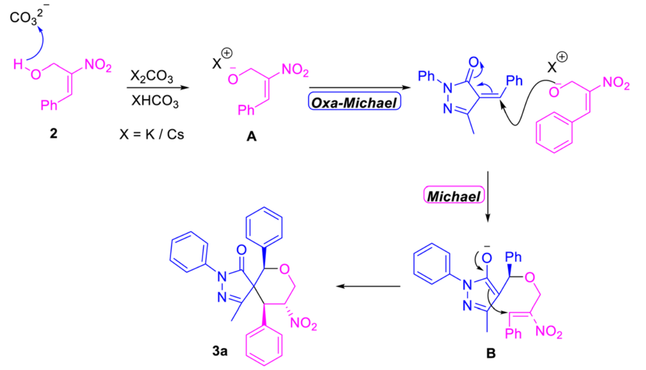
Most of the annulation reactions using MBH adducts involve the use of inorganic bases for proton abstraction, in line with a previous literature report,[23] and in the current work a plausible mechanism for the construction of spiropyrazolone tetrahydropyran scaffolds was derived. According to this proposed mechanism, the initial reaction of the alkali carbonate serving as a base (*i.e.*, K_2CO_3/Cs_2CO_3) with MBH alcohol generated the nucleophilic oxygen intermediate **A**. Attack by intermediate **A** from the "rear" position onto the benzylic carbon of α-arylidine pyrazolone *via* an oxa-Michael reaction generated a new O–C bond. And finally according to the proposed mechanism, further rearrangement of the resulting enol to a ketone and subsequent attack on the electrophilic olefinic site of MBH alcohol *via* formal [4 + 2] annulation resulted in the formation of a new C–C bond through a Michael reaction (Scheme 4). *In situ* Raman studies carried out for the reaction mixture shows the presence of keto group (*i.e.* 1495 cm^{-1}) of α-arylidene pyrazolone at the beginning of the reaction. This corresponding peak of 1495 cm^{-1} gradually disappeared after the initial oxa-Michael addition to form intermediate **B**. The intermediate **B** on reaction with benzyl bromide resulted in the disappearance of corresponding keto group peak, before completion of the final cyclisation *via* Michael Addition (S5 page of ESI†).



Scheme 2 Gram scale synthesis of spiro pyrazolone tetrahydropyrans 3a and 5a.



Scheme 3 Approaching a triple cascade for the construction of spiro pyrazolone tetrahydropyran in a three-component manner.



Scheme 4 Plausible reaction mechanism for the synthesis of spiro pyrazolone tetrahydropyrans.

Conclusions

In conclusion, the 1,4 ambiphilicity of β-nitro-styrene-derived MBH alcohols was investigated for achieving an efficient synthesis of tetrahydrospiropyrazolones *via* formal [4 + 2] cyclization at room temperature within 1 h. β-Nitro-styrene-derived 1° MBH alcohol gave tetrasubstituted spiropyrazolones when using K_2CO_3 whereas 2° MBH alcohol gave fully substituted spiropyrazolones when using Cs_2CO_3. The reaction tolerated various electron-withdrawing and electron-donating groups on the aryl ring of the arylidene pyrazolone as well as β-nitro-styrene-derived MBH alcohols to result in the desired products in high yields. Organocatalytic synthesis using quinine-derived thiourea catalyst resulted in desired spiropyrazolones with >94% enantiomeric excess and >20 : 1 dr. Interestingly, a triple-cascade three-component reaction produced the same spiropyrazolone tetrahydropyrans *via* the Knoevenagel/oxa-Michael/Michael process.

Author contribution

All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by Yeruva Pavankumar Reddy. Shaik Anwar contributed additional analysis required to address the comments and issues from the reviewers. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

SA thanks DST-SERB for providing the financial support under a Fast Track scheme (SB/FT/CS/079-2014). We are indebted to Vignan's Foundation for Science, Technology and Research for providing research facilities at CoExAMMPC.

Notes and references

1 (*a*) M. S. Chande, P. A. Barve and V. Suryanarayan, *J. Heterocycl. Chem.*, 2007, **44**, 49–53; (*b*) S. Wu, Y. Li, G. Xu, S. Chen, Y. Zhang, N. Liu, G. Dong, C. Miao, H. Su, W. Zhang and C. Sheng, *Eur. J. Med. Chem.*, 2016, **115**, 141; (*c*) I. Schlemminger, B. Schmidt, D. Flockerzi, H. Tenor, C. Zitt, A. Hatzelmann, D. Marx, C. Braun, R. Kuelzer, A. Heuser, H.-P. Kley and G. J. Sterk, Germany Patent WO2010055083, 2008; (*d*) B. Schmidt, C. Scheufler, J. Volz, M. P. Feth, R.-P. Hummel, A. Hatzelmann, C. Zitt, A. Wohlsen, D. Marx, H.-P. Kley, D. Ockert, A. Heuser, J. A. M. Christiaans, G. J. Sterk and W. M. P. B. Menge, Germany Patent WO2008138939, 2010.

2 J.-Y. Liu, J. Zhao, J.-L. Zhang and P.-F. Xu, *Org. Lett.*, 2017, **19**, 1846.

3 J.-H. Li and D.-M. Du, *Chem. Asian J.*, 2004, **9**, 3278.

4 X.-L. Zhang, C.-K. Tang, A.-B. Xia, K.-X. Feng, X.-H. Du and D.-Q. Xu, *Eur. J. Org. Chem.*, 2017, **2017**, 3152.

5 J.-H. Li, H. Wen, L. Liu and D.-M. Du, *Eur. J. Org. Chem.*, 2016, **2016**, 2492.

6 B. Mondal, R. Maity and S. Pan, *J. Org. Chem.*, 2018, **83**, 8645.

7 (*a*) S. Meninno, A. Roselli, A. Capobianco, J. Overgaard and A. Lattanzi, *Org. Lett.*, 2017, **19**, 5030; (*b*) Y. Lin, B.-L. Zhao and D.-M. Du, *J. Org. Chem.*, 2019, **84**, 10209.

8 C. Wang, D. Wen, H. Chen, Y. Deng, X. Liu, X. Liu, L. Wang, F. Gao, Y. Guo, M. Sun, K. Wang and W. Yan, *Org. Biomol. Chem.*, 2019, **17**, 5514.

9 A. Zea, R. Alba, A. Mazzanti, A. Moyanoa and R. Rios, *Org. Biomol. Chem.*, 2011, **9**, 6519.

10 J.-X. Zhang, N.-K. Li, Z.-M. Liu, X.-F. Huang, Z.-C. Geng and X.-W. Wang, *Adv. Synth. Catal.*, 2013, **355**, 797.

11 (*a*) H. Zhang, H. Lv and S. Ye, *Org. Biomol. Chem.*, 2013, **11**, 6255; (*b*) J. Li and D. Du, *Chin. J. Chem.*, 2015, **33**, 418.

12 S. Wang, C. Rodriguez-Escrich and M. Pericàs, *Org. Lett.*, 2016, **18**, 556.

13 (*a*) C. Zhao, K. Shi, G. He, Q. Gu, Z. Ru, L. Yang and G. Zhong, *Org. Lett.*, 2019, **21**, 7943; (*b*) W. Yang, Y. Zhang, S. Qiu, C. Zhao, L. Zhang, H. Liu, L. Zhou, Y. Xiao and H. Guo, *RSC Adv.*, 2015, **5**, 62343; (*c*) P. Sun, C.-Y. Meng, F. Zhou, X.-S. Li and J.-W. Xie, *Tetrahedron*, 2014, **70**, 9330.

14 (*a*) B.-D. Cui, S.-W. Li, J. Zuo, Z.-J. Wub, X.-M. Zhanga and W.-C. Yuana, *Tetrahedron*, 2014, **70**, 1895; (*b*) N. Chen, L. Zhu, L. Gan, Z. Liu, R. Wang, X. Cai and X. Jiang, *Eur. J. Org. Chem.*, 2018, **2018**, 2939.

15 (*a*) L. Liu, Y. Zhong, P. Zhang, X. Jiang and R. Wang, *J. Org. Chem.*, 2012, **77**, 10228; (*b*) A.-B. Xia, X.-L. Zhang, C.-K. Tang, K.-X. Feng, X.-H. Dua and D.-Q. Xu, *Org. Biomol. Chem.*, 2017, **15**, 5709; (*c*) s. wang, J. Izquierdo, R.-E. Carles and A. Pericàs, *ACS Catal.*, 2017, **7**, 2780; (*d*) J.-Y. Liu, J. Zaho, J.-L. Zhang and P.-F. Xu, *Org. Lett.*, 2017, **19**, 1846.

16 B. Mao, H. Liu, Z. Yan, Y. Xu, J. Xu, W. Wang, Y. Wu and H. Guo, *Angew. Chem., Int. Ed.*, 2020, **59**, 11316.

17 D. Hack, Alexander B. Durr, K. Deckers, P. Chauhan, N. Seling, L. Rubenach, L. Martens, G. Raabe, F. Schoenebeck and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**(5), 1797–1800.

18 W. Zheng, J. Zhang, S. Liu and Z. Miao, *RSC Adv.*, 2015, **5**, 91108.

19 M. Amireddy and K. Chen, *RSC Adv.*, 2016, **6**, 77474.

20 (*a*) Y. P. Reddy, V. Gudise, P. C. Settipalli and S. Anwar, *ChemistrySelect*, 2021, **6**, 4456; (*b*) V. Gudise, P. C. Settipalli, E. K. Reddy and S. Anwar, *Eur. J. Org. Chem.*, 2019, **2019**, 2234.

21 (*a*) V. Gudise, P. C. Settipalli, Y. P. Reddy and S. Anwar, *ChemistrySelect*, 2021, **6**, 13589; (*b*) S. Anwar, L.-T. Lin, V. Srinivasadesikan, V. B. Gudise and K. Chen, *RSC Adv.*, 2021, **11**, 38648; (*c*) P. C. Settipalli, Y. P. Reddy, V. Gudise and S. Anwar, *ChemistrySelect*, 2021, **6**, 47.

22 CCDC 2215596 for **3h**, possess the crystallographic data for this manuscript. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* **www.ccdc.cam.ac.uk/data_request/cif**.

23 (*a*) E. Gopi and I. N. N. Namboothiri, *J. Org. Chem.*, 2014, **79**, 7468; (*b*) T. Kumar, S. Mobin and I. N. N. Namboothiri, *Tetrahedron*, 2013, **69**, 4964–4972; (*c*) W.-Y. Huang, Y.-C. Chen and K. Chen, *Chem. Asian J.*, 2012, **7**, 688–691.