


 Cite this: *RSC Adv.*, 2025, 15, 2602

One-pot reaction of 3-vinylchromones, aromatic aldehydes, and ammonium acetate: an efficient approach to highly functionalized 1,6-dihydropyridine derivatives†

 Behnaz Farajpour,^{‡a} Marzie Kakaie,^{‡a} Faig H. S. Hussain,^{Ⓜb} Fataneh Rakae,^a Fatemeh Moradkhani^c and Morteza Shiri^{Ⓜ*a}

In this work, we present an efficient strategy for the straightforward synthesis of functionalized 1,6-dihydropyridine derivatives *via* a three-component reaction of 3-vinylchromones, aromatic aldehydes, and ammonium acetate. A tandem procedure including *in situ* NH aldimine formation/Michael-type addition/opening of the pyrone ring/isomerization/ 6π -electrocyclization/[1,5]-H shift allows rapid access to a series of dihydropyridines bearing an *ortho*-hydroxybenzoyl and a benzoyl scaffold in good yields. Readily available precursors, simple heating conditions, and operational simplicity are some highlighted advantages of this transformation.

 Received 4th November 2024
 Accepted 16th January 2025

DOI: 10.1039/d4ra07863b

rsc.li/rsc-advances

Introduction

Dihydropyridines (DHPs) represent an interesting family of heterocycles based on the pyridine ring.¹ Five isomeric structures are possible for this class of organic compounds.² Regarding the scaffold of dihydropyridines, 1,4- and 1,2- or 1,6-DHPs constitute the most populated group.³ Although 1,4-DHPs have garnered much interest due to their extensive biological and pharmacological activities,⁴ 1,2-DHPs are mostly known as versatile precursors to complex organic functional materials and are frequently employed as building blocks.⁵

For example, 1,2-DHPs can be used as cyclic aza-dienes in the Diels-Alder reaction for the synthesis of isoquinuclidines (2-azabicyclo[2.2.2]octanes).⁶ Notably, isoquinuclidines are valuable synthons for the synthesis of some privileged medicinal scaffolds such as oseltamivir phosphate.⁷ More specifically, the isoquinuclidine ring system is present in pharmacologically relevant molecules such as the alkaloids ibogaine, catharanthine, and dioscorine (Fig. 1).⁸ Consequently, the development of novel and efficient methods for synthesizing

substituted 1,2-dihydropyridines is an interesting topic for organic chemists. Notably, various synthetic routes for the preparation of substituted 1,2-DHPs have been reviewed in 2013 by Silva and co-workers.⁹ Moreover, several graceful methodologies for the synthesis of 1,2-dihydropyridine derivatives have been developed in the past years.¹⁰ For example, Tejedor and co-workers reported the synthesis of substituted 1,2-DHPs through a microwave-assisted domino reaction of propargyl vinyl ethers and primary amines (Scheme 1A).¹¹ The Lewis acid-catalyzed annulation of propargylic alcohols with (*E*)-3-amino-3-phenylacrylonitriles for the synthesis of functionalized 1,2-dihydropyridine derivatives was illustrated by Zhao's group (Scheme 1B).¹² Antonchick *et al.* demonstrated the metal-free synthesis of substituted 1,2-dihydropyridines with quaternary stereogenic centers using a cascade aza-Wittig/ 6π -

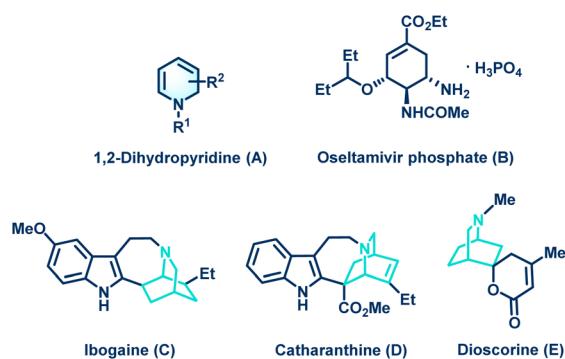


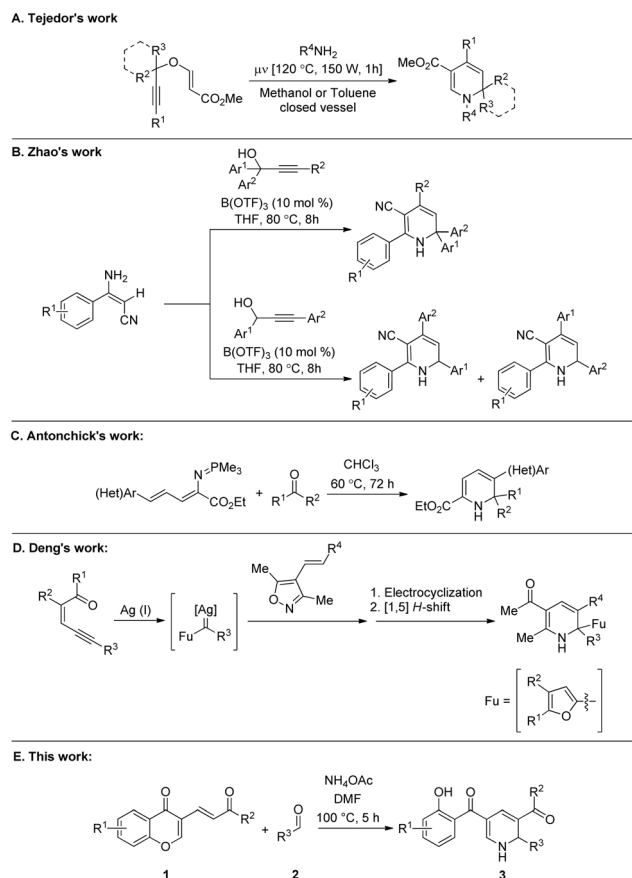
Fig. 1 Structures of 1,2-dihydropyridines (A), oseltamivir phosphate (B), and some pharmaceutically active molecules containing the isoquinuclidine unit (C–E).

^aDepartment of Organic Chemistry, Faculty of Chemistry, Alzahra University, Vanak, Tehran 1993893973, Iran. E-mail: mshiri@alzahra.ac.ir

^bMedical Analysis Department, Applied Science Faculty, Tishk International University, Erbil 44001, Kurdistan Region, Iraq

^cDepartment of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran P94V+8MF, Iran

[†] Electronic supplementary information (ESI) available. CCDC 2364260 and 2364261. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ra07863b>
[‡] These authors contributed equally.

Scheme 1 Synthesis of functionalized dihydropyridine derivatives.

Table 1 Survey on the conditions for the synthesis of **3a**^a

Entry	<i>x</i>	$[\text{NH}_4]^+$ (<i>y</i>)	Solvent (3 mL)	Temperature (°C)	Time (h)	Yield (%) ^b
1	1	NH ₄ OAc (2)	MeCN	25	24	0
2	1	NH ₄ OAc (2)	MeCN	80	16	59
3	1	NH ₄ OAc (2)	EtOH	80	15	57
4	1	NH ₄ OAc (2)	DMSO	100	10	72
5	1	NH ₄ OAc (2)	DMF	100	10	77
6	1	NH ₄ OAc (2)	CHCl ₃	60	24	Trace
7	1	NH ₄ OAc (2)	<i>n</i> -hexane	70	24	Trace
8	1	NH ₄ OAc (2)	THF	65	24	Trace
9	1	NH ₄ Cl (2)	DMF	100	24	14
10	1	(NH ₄) ₂ SO ₄ (2)	DMF	100	24	11
11	1	NH ₄ OAc (3)	DMF	100	9	81
12	1	NH ₄ OAc (4)	DMF	100	7	84
13	1	NH ₄ OAc (5)	DMF	100	7	79
14	1.5	NH ₄ OAc (4)	DMF	100	5	89
15	2	NH ₄ OAc (4)	DMF	100	5	80

^a Reaction conditions: a mixture of **1a** (1 equiv.), **2a** (*x* equiv.), and ammonia source (*y* equiv.) in the mentioned solvent (3 mL) was magnetically stirred at the mentioned temperature in an oil bath. The target product was purified by column chromatography on silica gel using *n*-hexane/EtOAc (5 : 1 v/v) as the eluent. ^b Isolated yields.

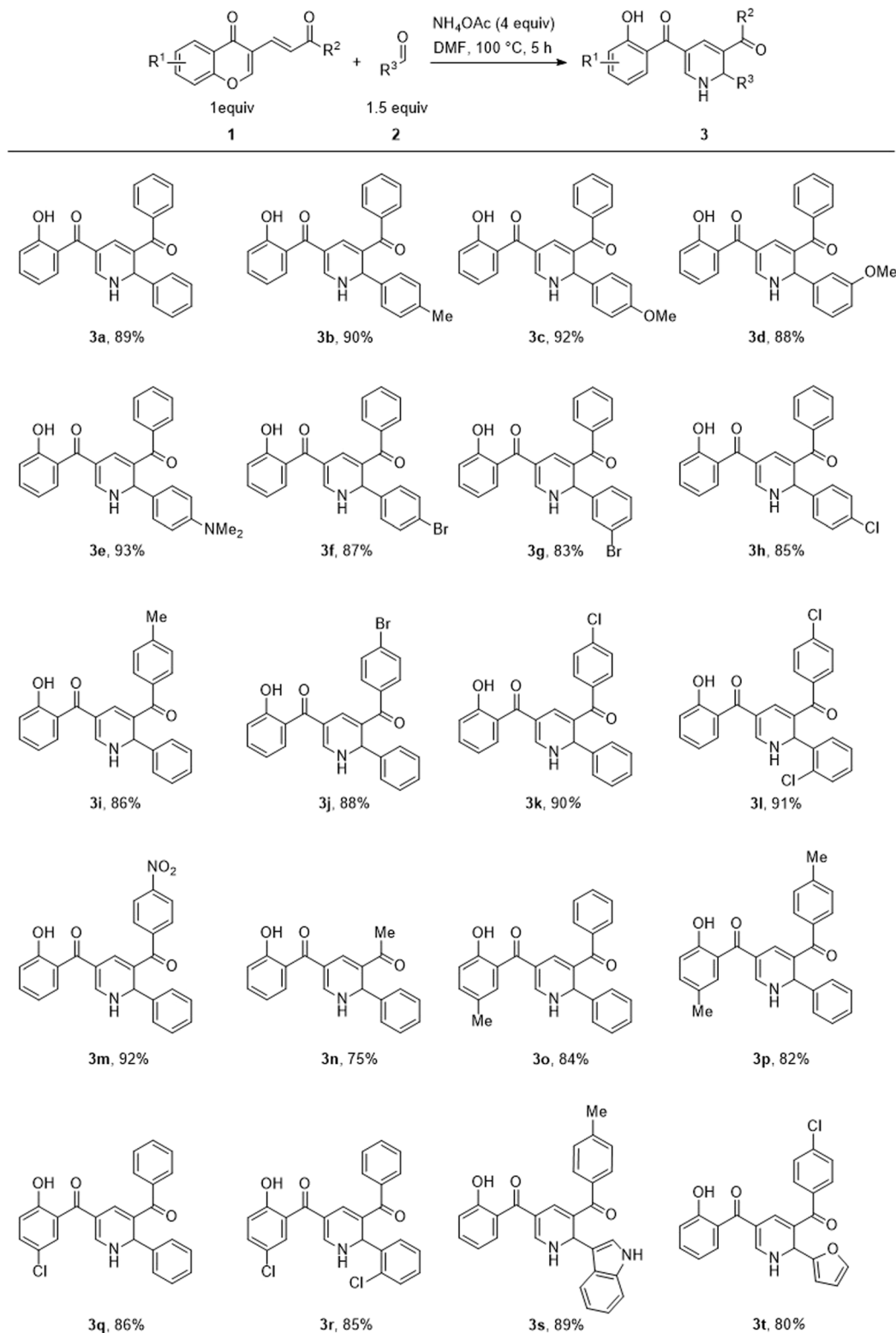
electrocyclization process (Scheme 1C).¹³ Very recently, Deng's group disclosed the elegant synthesis of functionalized 1,2-dihydropyridines *via* a silver(I)-catalyzed tandem reaction of enynones and 4-alkenyl isoxazoles (Scheme 1D).¹⁴ Although these reported methods make a considerable contribution for the construction of structurally diverse 1,2-dihydropyridine scaffolds, some of them are limited by the employment of sensitive or expensive prefunctionalized starting materials, transition-metal catalysts, and tedious multistep transformations. In this regard, the development of efficient, innovative, and simple strategies to overcome these limitations is highly desirable. Notably, chromone derivatives¹⁵ occupy an important position in the preparation of various organic scaffolds due to their ability to undergo ring-opening reactions.¹⁶ Having interest in developing novel routes for the construction of privileged organic architectures,¹⁷ herein we considered the use of aldehydes and ammonium acetate as reaction partners to 3-vinyl chromones^{16e} for the preparation of functionalized dihydropyridine derivatives (Scheme 1E).

Interestingly, this multicomponent strategy incorporates benzoyl and *ortho*-hydroxybenzoyl frameworks into a 1,2-dihydropyridine core. Furthermore, inexpensive and available materials, simple heating conditions, and satisfactory yields are some highlighted advantages of this practical route.

Results and discussion

We started our studies by evaluating the reaction of 3-vinyl chromone **1a** (1 equiv.), benzaldehyde **2a** (1 equiv.), and





Scheme 2 Synthesis of various substituted dihydropyridine derivatives.

ammonium acetate (2 equiv.) in acetonitrile under an ambient atmosphere. When the reaction was run at room temperature, the starting materials remained unreacted and small quantities of by-products were formed (Table 1, entry 1). Gratifyingly, clean conversion was observed upon increasing the reaction

temperature to 80 °C and product **3a** was generated in 59% yield (entry 2).

Encouraged by this initial result, different solvents were screened to optimize the reaction conditions. Compared with acetonitrile, ethanol afforded a comparative yield (entry 3).



A significant improvement in the reaction yield to 72% and the reaction time to 10 h was achieved by using dimethyl sulfide (DMSO) as the solvent by heating the reaction to 100 °C (entry 4). Furthermore, the reaction yield was marginally increased, from 72% to 77%, by changing the solvent from DMSO to dimethylformamide (DMF) (entry 5). Notably, some solvents, including chloroform, *n*-hexane, and tetrahydrofuran (THF), proved to be unusable for this process (entries 6–8). With the aim of further improving the reaction yield, various ammonia sources were evaluated. Results revealed that ammonium acetate is the best ammonia source for this reaction (entries 9 and 10). Further research showed that the amounts of starting materials are crucial for this transformation (entries 11–15), and the best result, 89% yield, was gained when the ratio of 3-vinyl chromone **1a**, benzaldehyde **2a**, and ammonium acetate was adjusted to 1 : 1.5 : 4. Therefore, the conditions of entry 14 were determined as the optimal conditions.

To gain insight into the versatility of this transformation, we set out to explore the reaction scope using various aldehydes and 3-vinyl chromone derivatives under the optimized conditions (Scheme 2). We first investigated the reaction efficiency with respect to diverse benzaldehyde derivatives. The results revealed that various substituted benzaldehydes, possessing electron-donating or weak electron-withdrawing substituents, were tolerated in this process, affording the desired products in good yields (**3b–3h**, 83–93%). However, for benzaldehydes with strong electron-withdrawing groups (CN, NO₂), the desired products were not formed. To further verify the generality of the reaction, aliphatic aldehydes such as butyraldehyde and decyl aldehyde were tested, but the target products were formed in trace amounts. These results could be related to the intrinsically lower stability of aliphatic aldimines due to their susceptibility to decomposition, self-condensation, and imine–enamine tautomerization.¹⁸ Subsequently, the scope of 3-vinylchromones was explored. To our delight, differently substituted 3-vinylchromones, possessing various *R*¹ and *R*² substituents, were compatible with this process and were successfully converted to the desired products (**3i–3r**, 75–92%). The developed strategy was also effective for some heterocyclic aldehydes including 3-formyl indole and 2-formyl furan delivering the products **3s** and **3t** in 89% and 80% yield, respectively. In the case of other heterocyclic aldehydes, including 2-formyl indole, 2-formyl pyrrole, 4-chloro-3-formyl coumarin, and 2-chloro-3-formyl quinoline, several overlapping spots were formed and the isolation process was very difficult. To investigate the synthetic utility of this method, the gram-scale synthesis of **3a** was explored. In this regard, the reaction of 3-vinylchromone **1a** (4 mmol, 1104 mg), benzaldehyde **2a** (6 mmol, 636 mg), and ammonium acetate (16 mmol, 1233 mg) proceeded well, affording the desired product **3a** in 80% yield (1219 mg) without a significant loss of efficiency compared to the small-scale experiment (89% yield). The structures of the products were characterized by high-resolution mass spectrometry (HRMS) analysis, and nuclear magnetic resonance (NMR). Moreover, the structure of **3l** was undeniably elucidated by using X-ray crystallographic analysis. Interestingly, in the crystallization process, we faced with the

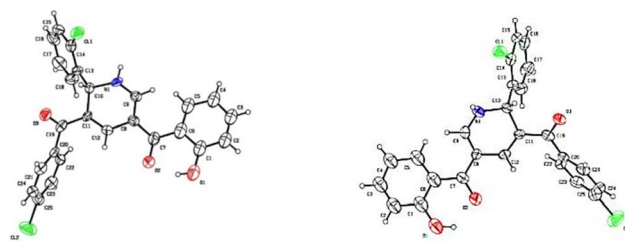
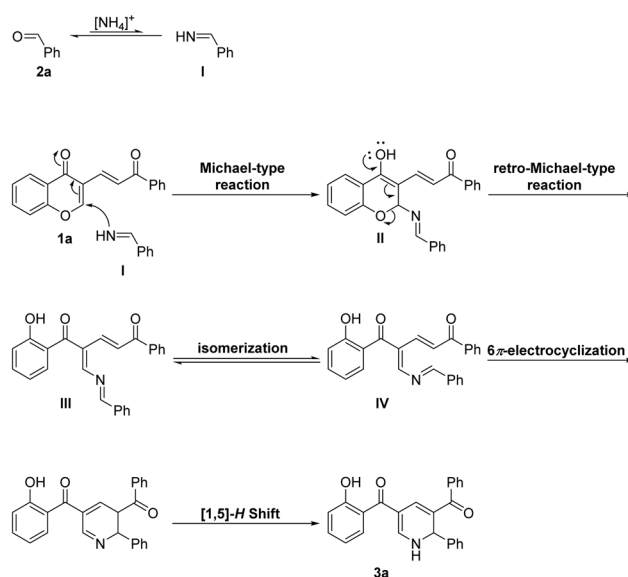


Fig. 2 ORTEP plot for the crystal structure of **3l-R** enantiomer (left) and **3l-S** enantiomer (right) (CCDC 2364260 and 2364261). Thermal ellipsoids are at 30% probability level.

spontaneous resolution of enantiomers. Therefore, we reported the crystal structure of both in this paper (Fig. 2). Based on the above results and related literature,¹⁹ a putative reaction mechanism is depicted in Scheme 3 (with **3a** as the example). The reaction begins with the formation of NH aldimine intermediate **I** through the condensation of **2a** with ammonia. The *in situ* formed intermediate **I** then reacts with 3-vinylchromone **1a** to provide intermediate **II** via a Michael-type reaction.

The process is followed by the opening of the pyrone ring in **II** to deliver 2-aza-triene intermediate **III**. In continue, the *s-trans*, *s-cis* intermediate **III** should be converted to the cyclization-reactive *s-cis*, *s-cis* intermediate **IV** in order to undergo 6 π -electrocyclization reaction. Notably, the conformer **IV** is thermodynamically unfavored and can be formed under thermal conditions. The subsequent thermal 6 π -electrocyclization of intermediate **IV** followed by a [1,5]-H Shift¹³ process affords final product **3a**.

In summary, an unprecedented catalyst-free reaction of 3-vinyl-4-chromones, aromatic aldehydes, and ammonium acetate has been developed.



Scheme 3 Proposed reaction mechanism for the formation of **3a**.

This one-pot transformation, carried out under simple heating conditions, provides access to substituted dihydropyridine derivatives in synthetically useful yields. The overall process (formation of one C–C bond and two C–N bonds) may include the following steps: NH aldimines formation/Michael-type addition/opening of the pyrone ring/isomerization/6 π -electrocyclization/[1,5]-H shift.

Furthermore, the presence of various substituents around the dihydropyridine core could furnish attractive points of postfunctionalization to afford a series of useful compounds that are difficult to prepare with other methods.

Further studies probing the usefulness of this strategy and synthetic applications of the products are ongoing in our laboratory.

Data availability

The data supporting the findings of this study are available within the article and ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Alzahra University and the Iran National Science Foundation (INSF) for financial support.

Notes and references

- U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1.
- R. M. Vala and H. M. Patel, *Adv. Heterocycl. Chem.*, 2023, **141**, 179.
- V. K. Sharma and S. K. Singh, *RSC Adv.*, 2017, **7**, 2682.
- N. Edraki, A. R. Mehdipour, M. Khoshneviszadeh and R. Miri, *Drug Discov. Today*, 2009, **14**, 1058.
- S. Duttwyler, S. Chen, C. Lu, B. Q. Mercado, R. G. Bergman and J. A. Ellman, *Angew. Chem.*, 2014, **126**, 3958.
- (a) O. Songis, C. Didierjean, C. Laurent, J. Martinez and M. Calmès, *Eur. J. Org. Chem.*, 2007, **2007**, 3166; (b) M. Sellstedt, H. Dang, G. K. Prasad, U. Sauer and F. Almqvist, *Eur. J. Org. Chem.*, 2013, **2013**, 7476; (c) R. M. Martin, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2013, **15**, 444.
- (a) H. Nakano, K. Osone, M. Takeshita, E. Kwon, C. Seki, H. Matsuyama, N. Takano and Y. Kohari, *Chem. Commun.*, 2010, **46**, 4827; (b) N. Satoh, T. Akiba, S. Yokoshima and T. Fukuyama, *Angew. Chem., Int. Ed.*, 2007, **46**, 5734.
- (a) M. Ishikura, T. Abe, T. Choshih and S. Hibino, *Nat. Prod. Rep.*, 2013, **30**, 694; (b) G. Kumar Jana, S. Paul and S. Sinha, *Org. Prep. Proced. Int.*, 2011, **43**, 541; (c) M. O. Faruk Khan, M. S. Levi, C. R. Clark, S. Y. Ablordeppey, S.-L. Law, N. H. Wilson and R. F. Borne, *Stud. Nat. Prod. Chem.*, 2008, **34**, 753; (d) L. Moisan, P. Thuery, M. Nicolas, E. Doris and B. Rousseau, *Angew. Chem., Int. Ed.*, 2006, **45**, 5334; (e) P. Ramaraju, A. P. Pawar, E. Iype, N. A. Mir, S. Choudhary, D. K. Sharma and K. Kant, *J. Org. Chem.*, 2019, **84**, 12408; (f) X. You, Y. Yao, P. Liu, L. Chen, Y. Xie, G. Li and L. Hong, *J. Org. Chem.*, 2024, **89**, 3635.
- E. M. P. Silva, P. A. M. M. Varandas and A. M. S. Silva, *Synthesis*, 2013, **45**, 3053.
- (a) H. Dai, S. Yu, W. Cheng, Z.-F. Xu and C.-Y. Li, *Chem. Commun.*, 2017, **53**, 6417; (b) Y.-B. Xie, S.-P. Ye, W.-F. Chen, Y.-L. Hu, D.-J. Li and L. Wang, *Asian J. Org. Chem.*, 2017, **6**, 746; (c) A. Heusler, J. Fliege, T. Wagener and F. Glorius, *Angew. Chem., Int. Ed.*, 2021, **60**, 13793; (d) P. Li, S. Wang, N. Tian, H. Yan, J. Wang and X. Song, *Org. Biomol. Chem.*, 2021, **19**, 3882; (e) K. Jayabal, D. Elumalai, S. Leelakrishnan, S. Bhattacharya, V. Rengarajan, T. Kannan and S.-C. Chuang, *ACS Omega*, 2022, **7**, 43856.
- D. Tejedor, L. Cotos, G. Méndez-Abt and F. García-Tellado, *J. Org. Chem.*, 2014, **79**, 10655.
- L.-J. Du, Y. Zhang, H.-Y. Zhang, G. Yin, X.-Y. Wang, J. Zhao and Y.-P. Han, *J. Org. Chem.*, 2020, **85**, 9863.
- V. Polychronidou, A. Krupp, C. Strohmann and A. P. Antonchick, *Org. Lett.*, 2021, **23**, 6.
- H. Peng, Y. Zhang and G. Deng, *J. Org. Chem.*, 2023, **88**, 7038.
- (a) A. Levai and J. Jeko, *J. Heterocycl. Chem.*, 2004, **41**, 439; (b) A.-T. Dang, D. O. Miller, L. N. Dawe and G. J. Bodwell, *Org. Lett.*, 2008, **10**, 233; (c) S. Wang, Y. Zhang, C. Liang, Y. Zhang, R. Zhan and H. Huang, *Org. Lett.*, 2023, **25**, 8269.
- (a) A. Levai and J. Jeko, *J. Heterocycl. Chem.*, 2002, **39**, 1333; (b) A. Levai, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, I. Alkorta, J. Elguero and J. Jeko, *Eur. J. Org. Chem.*, 2004, **2004**, 4672; (c) X.-J. Huang, Y. Tao, Y.-K. Li, X.-Y. Wu and F. Sha, *Tetrahedron*, 2016, **72**, 8565; (d) S. Sultana, S. M. B. Maezono, M. S. Akhtar, J.-J. Shim, Y.-J. Wee, S. H. Kim and Y. R. Lee, *Adv. Synth. Catal.*, 2018, **360**, 751; (e) M. Giardinetti, N. I. Jessen, M. L. Christensen and K. A. Jorgensen, *Chem. Commun.*, 2019, **55**, 202; (f) A. Alizadeh and A. Bagherinejad, *Mendeleev Commun.*, 2023, **33**, 401; (g) G. Haas, J. L. Stanton and A. V. Sprecher, *J. Heterocycl. Chem.*, 1981, **18**, 607; (h) E. R. Baral, K. Sharma, M. S. Akhtar and Y. R. Lee, *Org. Biomol. Chem.*, 2016, **14**, 10285; (i) Z. Chen, Z. Dai, Z. Zhu and X. F. Yang, *Tetrahedron Lett.*, 2017, **58**, 1258; (j) L. M. Sanchez, A. G. Sathicq, J. L. Jios, G. T. Baronetti, H. J. Thomas and G. P. Romanelli, *Tetrahedron Lett.*, 2011, **52**, 4412; (k) L. M. Sanchez, G. Pasquale, A. Sathicq, D. Ruiz, J. Jios, A. L. Ferreira de Souza and G. P. Romanelli, *Heteroat. Chem.*, 2016, **27**, 243.
- (a) B. Farajpour, R. Heydarzadeh, F. H. S. Hussain, B. Notash, P. Mirzaei and M. Shiri, *J. Org. Chem.*, 2024, **89**, 4375; (b) A. Alizadeh, B. Farajpour, T.-O. Knedel and C. Janiak, *J. Org. Chem.*, 2021, **86**, 574; (c) B. Farajpour and A. Alizadeh, *J. Org. Chem.*, 2022, **87**, 13837; (d) B. Farajpour, G. B. Alizadeh, S. Majedi, F. Moradkhani, S. Majedi, B. Notash, B. Hosseindoust and M. Shiri, *ACS Omega*, 2024, **9**, 26607; (e) M. Shiri, B. Farajpour, Z. Bozorgpour-Savadjani, S. A. Shintre, N. A. Koorbanally, H. G. Kruger and B. Notash, *Tetrahedron*, 2015, **71**, 5531; (f) M. Shiri, M. A. Zolfigol and R. Ayazi-Nasrabadi,



- Tetrahedron Lett.*, 2010, **51**, 264–268; (g) M. Shiri, M. M. Heravi and B. Soleymanifard, *Tetrahedron*, 2012, **68**, 6593–6650; (h) M. Shiri, S. Z. Mirpour-Marzoni, Z. Bozorgpour-Savadjani, B. Soleymanifard and H. G. Kruger, *Monatsh. Chem.*, 2014, **145**, 1947–1952.
- 18 W.-S. Li, T.-S. Kuo, M.-C. Hsieh, M.-K. Tsai, P.-Y. Wu and H.-L. Wu, *Org. Lett.*, 2020, **22**, 5675.
- 19 (a) J. Yan, M. Cheng, F. Hu and Y. Hu, *Org. Lett.*, 2012, **14**, 3206; (b) Y.-F. Zhang, W.-D. Duan, J. Chen and Y. Hu, *J. Org. Chem.*, 2019, **84**, 4467; (c) H. S. Sim, H. D. Khanal and Y. R. Lee, *J. Org. Chem.*, 2022, **87**, 12890; (d) E. Meghrazi Ahadi, A. Abbasi Kejani, H. Khosravi, V. Fathi Vavsari, S. Balalaie, F. Rominger and H. R. Bijanzadeh, *J. Org. Chem.*, 2021, **86**, 12705.

