



Cite this: *Org. Biomol. Chem.*, 2024, 22, 8720

Received 14th July 2024,
Accepted 20th September 2024
DOI: 10.1039/d4ob01168f

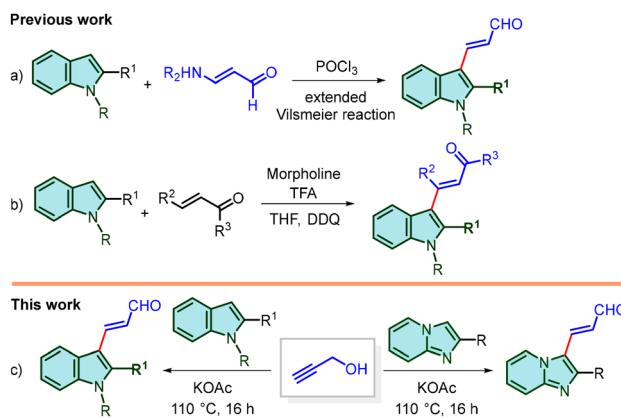
rsc.li/obc

A simple and straightforward method has been developed to access distinctly substituted β -(3-indolyl)acroleins and β -(imidazo[1,2-*a*]pyridin-3-yl)acroleins using propargyl alcohol as an acrolein equivalent. A broad substrate scope, good yields, easily accessible substrates, and metal-free conditions are the salient features of the developed methodology. This work contributes to a significant advancement in the sustainable synthesis of functionalized acroleins.

Among the nitrogen-containing heterocycles, indoles and imidazo[1,2-*a*]pyridines are well-known scaffolds widely found in many naturally occurring and synthetic compounds.¹ A myriad of indole and imidazopyridine-based compounds have been studied for a broad range of biological and pharmacological activities such as antimicrobial, antiviral, antiprotozoal, anti-inflammatory, anti-ulcer, and anticancer activities.² These heterocycles are essential pharmacophores of several marketed drugs such as indomethacin, atevirdine, delavirdine, arbidol, panobinostat, alpidem, zolpidem, olprinone, and minodronic acids.^{1c,3} Owing to the therapeutic applications of these heterocyclic motifs, the synthesis and functionalization of indoles⁴ and imidazo[1,2-*a*]pyridines⁵ has been a major area of focus and continues to be an important research area for chemists.

On the other hand, the acrolein moiety has been used as a highly active linker to design cytotoxic compounds.⁶ 3-(Coumarin-3-yl)acrolein derivatives have been evaluated as novel anticancer chemotherapeutic candidates with remarkable antiproliferative activity against various cancer cell lines.⁷ 3-(3-(4-Fluorophenyl)-1-isopropyl-1*H*-indol-2-yl)acrolein is a key intermediate of the anti-cholesterol fluvastatin drug.⁸ β -Substituted acroleins are also important intermediates for the construction of

complex molecular architectures.⁹ The presence of acrolein functionality on indoles and imidazo[1,2-*a*]pyridines would allow their easy transformations. For example, they could be key building blocks for the synthesis of various fused nitrogen heterocycles employing C–H functionalization¹⁰ and [4 + 2]-cycloaddition reactions.¹¹ The synthesis of 3-(indol-3-yl)acroleins is generally achieved by the Wittig reaction of indole-3-carbaldehydes and Wittig ylides.¹² It is notable that the synthesis of 3-(indol-3-yl)acroleins is quite challenging and there are only a few methods starting from indole (Scheme 1). In early days, 3-(indol-3-yl)acrolein was obtained employing an extended Vilsmeier reaction of indole with 3-methyl-3-phenylaminopropenal (Scheme 1a). Vanderwal and co-workers reported an interesting method for the preparation of 3-(indol-3-yl)acroleins by a ring-opening reaction of pyridinium salts, but the use of toxic BrCN and a narrow substrate scope limit its broad application.¹³ Jiao's group synthesized 3-(indol-3-yl)acroleins by morpholine-catalysed addition of indoles with α,β -unsaturated aldehydes followed by oxidation with DDQ (Scheme 1b).¹⁴ To the best of our knowledge, there is no report on the synthesis of β -(imidazo[1,2-*a*]pyridin-3-yl)acroleins.



^aDepartment of Chemistry, Birla Institute of Technology and Science, Pilani, Pilani Campus, Rajasthan, 333031, India. E-mail: anilkumar@pilani.bits-pilani.ac.in

^bDepartment of Chemistry, Birla Institute of Technology and Science, Pilani, Hyderabad Campus, Telangana, 500078, India

[†]Electronic supplementary information (ESI) available: Experimental procedures, analytical data, XRD data and copies of NMR (¹H & ¹³C). CCDC 2266943, 2266949 and 2266961. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ob01168f>

Scheme 1 Synthesis of β -(3-indolyl)acroleins and β -(imidazo[1,2-*a*]pyridin-3-yl)acroleins.



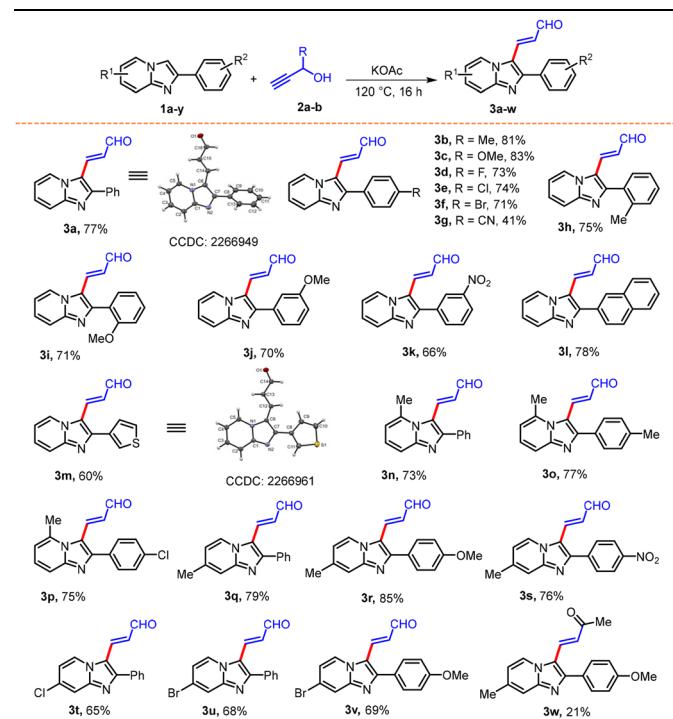
During our investigation on manganese-mediated *ortho*-alkenylation of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with propargyl alcohol (**2**), β -(2-phenylimidazo[1,2-*a*]pyridin-3-yl)acrolein (**3a**) was obtained in 15% yield as a side product (Table 1, entry 1). With this interesting result, we decided to optimize the reaction conditions to improve the yield of this acrolein derivative **3a** (Table 1). Initially, we varied the catalyst and **3a** was obtained in 18% yield along with **3a'** (33%) on using $\text{Mn}(\text{OAc})_2$, while the reaction failed with $\text{Mn}_2(\text{CO})_{10}$ (Table 1, entries 2 and 3). Interestingly, when the reaction was performed in the absence of THF using propargyl alcohol (**2**) as a solvent, **3a** (60%) was obtained as the major product (Table 1, entry 4). Moreover, the yield of **3a** increased slightly to 63% in the absence of the catalyst, indicating that the manganese catalyst has no role in the formation of **3a** (Table 1, entry 5). Among different acetates, the use of KOAc produced **3a** in 73% yield which further increased to 77% on increasing the amount of KOAc to two equivalents (Table 1, entries 5–8). No significant change in yield was noticed upon increasing the reaction temperature up to 150 °C; however, lowering the reaction temperature to 80 °C resulted in a decreased yield (59%) of **3a** (Table 1, entries 9 and 10). Finally, the reaction carried out in the absence of KOAc did not produce any product (Table 1, entry 11). Based on the above experimental results, KOAc (2 equiv.) in propargyl alcohol for 16 h at 120 °C were chosen as the optimum reaction conditions (Table 1, entry 8).

Having the optimal reaction conditions in hand, we shifted our focus to evaluate the scope and limitations of this method (Table 2). Imidazo[1,2-*a*]pyridines substituted with electron-donating groups (Me and OMe), halogens (F, Cl, and Br) and an electron-withdrawing group (CN) at the *para*-position of the C2-phenyl ring reacted smoothly to produce the corresponding substituted acrolein derivatives (**3a**–**3g**) in moderate to very

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst	Additive	Solvent	<i>t</i> (°C)	% Yield ^b	
					3a'	3a
1	$\text{MnBr}(\text{CO})_5$	NaOAc	THF	120	48	15
2	$\text{Mn}(\text{OAc})_2$	NaOAc	THF	120	33	18
3	$\text{Mn}_2(\text{CO})_{10}$	NaOAc	THF	120	Trace	—
4	$\text{MnBr}(\text{CO})_5$	NaOAc	2	120	Trace	60
5	—	NaOAc	2	120	—	63
6	—	KOAc	2	120	—	73
7	—	CsOAc	2	120	—	58
8	—	KOAc (2 equiv.)	2	120	—	77
9	—	KOAc (2 equiv.)	2	0	—	59
10	—	KOAc (2 equiv.)	2	150	—	74
11	—	—	2	120	—	—

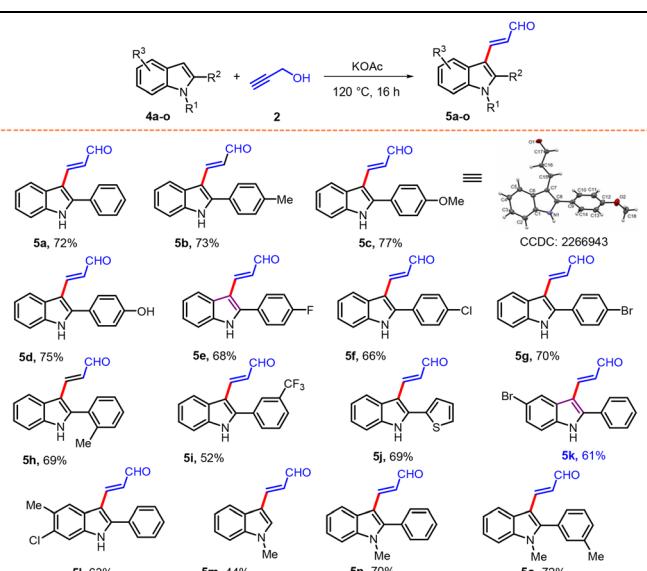
^a Reaction conditions: **1a** (0.52 mmol), **2** (2 mL), catalyst (10 mol%), additive (1.03 mmol, 2 equiv.), 16 h. ^b Isolated yield.

Table 2 Synthesis of β -(imidazo[1,2-*a*]pyridin-3-yl)acroleins^{a,b}

^a Reaction conditions: **1a** (0.52 mmol), **2** (2 mL), KOAc (1.03 mmol, 2 equiv.), 120 °C, 16 h. ^b Isolated yield.

good yields (41–83%). Higher yields of products were obtained from imidazopyridines with electron-donating groups on the C2-phenyl ring as compared with those having electron-withdrawing groups. This was further established by a one-pot competitive reaction of **1b** and **1e** with **2** which produced the corresponding products **3b** and **3e** in 5 : 3 ratios. Subsequently, reactions of **2** with *ortho*-substituted 2-arylimidazo[1,2-*a*]pyridines (**1h** and **1i**), *meta*-substituted 2-arylimidazo[1,2-*a*]pyridines (**1j** and **1k**), 2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine (**1l**) and 2-(thiophen-3-yl)imidazo[1,2-*a*]pyridine (**1m**) produced the desired acrolein derivatives (**3h**–**3m**) in good yields (60–75%). Notably, imidazo[1,2-*a*]pyridines (**1n**–**1v**) with substituents (Me and Br) on various positions of the imidazopyridine nucleus also reacted smoothly furnishing the expected acrolein derivatives (**3n**–**3v**) in moderate to very good yields (56–85%). The reaction of but-3-yn-2-ol (**2b**) with **1r** under standard conditions was sluggish and produced the corresponding alkenylated derivative **3w** only in 21% yield. Unfortunately, the reaction of 3-phenylprop-2-yn-1-ol (**2c**) with **1a** failed to produce the corresponding product under standard conditions. The structures of all the β -(imidazo[1,2-*a*]pyridin-3-yl)acrolein derivatives (**3**) were ascertained by IR, ¹H NMR, ¹³C NMR and HRMS analyses. Furthermore, the structures of **3a** (CCDC no. 2266949†) and **3m** (CCDC no. 2266961†) were unambiguously confirmed by single crystal X-ray diffractometer analysis.

Next, we extended the scope of the method to indoles. As can be noted from Table 3, the reaction of **2** with 2-arylindoles

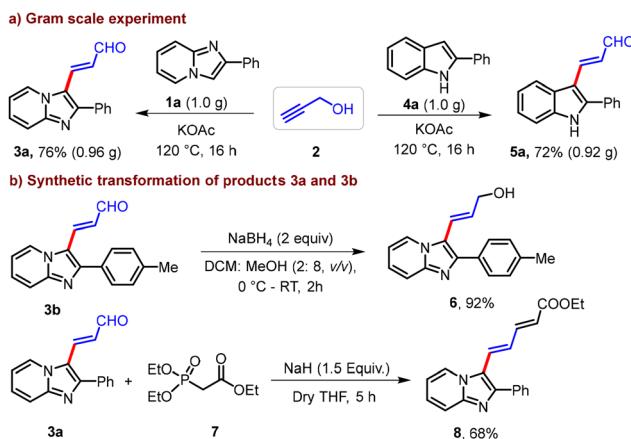
Table 3 Synthesis of β -(indol-3-yl)acroleins^{a,b}

^a Reaction conditions: 4 (0.52 mmol), 2 (2 mL), KOAc (1.03 mmol, 2 equiv.), 120 °C, 16 h. ^b Isolated yield.

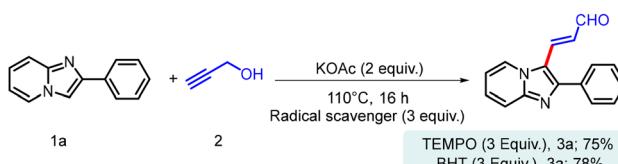
(4a-i) substituted with electron-donating groups (Me, OMe, and OH) and halogens (F, Cl and Br) at the *para*-position, a methyl group at the *ortho*-position and a CF₃ group at the *meta*-position of the C2-phenyl ring produced the corresponding β -(indol-3-yl)acroleins (5a-i) in moderate to good yields (52–77%). 2-(Thiophen-3-yl)indole (4j) on reaction with 2 produced the corresponding acrolein derivative 5j with 69% yield. Furthermore, indoles with substitutions at the C5-position (4k) and the C5, C6-position (4l) were found to be suitable substrates, leading to the formation of acrolein derivatives 5k and 5l in 61% and 63% yields, respectively. Additionally, *N*-methylindoles (4m-o) also reacted smoothly with 2 to produce the corresponding acrolein derivatives (5m-o) in moderate to good yields (44–72%). The structures of all the β -(indol-3-yl)acrolein derivatives (5) were ascertained by IR, ¹H NMR, ¹³C NMR and HRMS analyses and the structure of 5c (CCDC no. 2266943†) was unambiguously confirmed by single crystal X-ray diffractometer analysis.

The synthetic utility of the developed protocol is demonstrated by gram-scale synthesis and synthetic transformation of the product (Scheme 2). Keeping the ratios of the reagents consistent with the standard reaction, the reaction of 2 with 1a (1.0 g) and 4a (1.0 g) afforded 0.96 g (76%) of 3a and 0.92 g (72%) of 5a, respectively (Scheme 2a). Furthermore, reduction of 3b with NaBH₄ produced γ -(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)allyl alcohol (6) in 92% yield (Scheme 2b). Similarly, the reaction of 3a with phosphorus ylide (7) in the presence of NaH in dry THF for 5 h at 0 °C-RT afforded the corresponding conjugated alkene product 8 in 68% yield (Scheme 2b).

The presence of radical scavengers TEMPO and BHT (3 equivalents each) in the reaction of 1a and 2 did not suppress the yield of 3a (Scheme 3). The result obtained from the above



Scheme 2 Gram-scale experiment and synthetic transformation of products.



Scheme 3 Radical trapping experiment.

experiment suggests that the reaction does not follow a radical pathway. It is believed that the reaction proceeds *via* hydroarylation of propargyl alcohol followed by oxidation. More work on understanding the mechanism of this reaction is under progress in our lab.

Conclusions

In conclusion, we have developed a simple and straightforward method to access distinctly substituted β -(3-indolyl)acrolein and β -(imidazo[1,2-*a*]pyridin-3-yl)acrolein derivatives using propargyl alcohol as an acrolein equivalent. The salient features of this method are the use of readily available and easy-to-handle propargyl alcohol as an acrolein equivalent, good to high yields, a wide substrate scope, metal-free reaction conditions, and simple workup procedures. A wide range of synthetically useful functional groups such as Cl, Br, F, OMe, OH, CF₃, NO₂, and CN were tolerated well under these conditions. Furthermore, gram-scale synthesis also demonstrates that the method can be applied to bulk processes.

Author contributions

B. optimized the reaction conditions and prepared β -(imidazo[1,2-*a*]pyridin-3-yl)acroleins. S. prepared β -(indol-3-yl)acroleins. B., S., P. N. S. and V. N. S. recorded data, analysed and discussed the results with A. K. K. R. recorded and analysed single crystal data. A. K. supervised the project and wrote the

manuscript. All authors contributed to the manuscript and have approved the final version of the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank BITS Pilani and DST New Delhi for the NMR and HRMS facilities, respectively. B. thanks BITS Pilani for the institute fellowship.

References

- 1 (a) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, **18**, 6620–6662; (b) A. Garrido, G. Vera, P.-O. Delaye and C. Enguehard-Gueiffier, *Eur. J. Med. Chem.*, 2021, **226**, 113867; (c) T. V. Sravanti and S. L. Manju, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10.
- 2 N. Devi, D. Singh, K. R. Rawal, J. Bariwal and V. Singh, *Curr. Top. Med. Chem.*, 2016, **16**, 2963–2994.
- 3 S. Samanta, S. Kumar, E. K. Aratikatla, S. R. Ghorpade and V. Singh, *RSC Med. Chem.*, 2023, **14**, 644–657.
- 4 (a) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920; (b) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911; (c) K. Urbina, D. Tresp, K. Sipps and M. Szostak, *Adv. Synth. Catal.*, 2021, **363**, 2723–2739; (d) P. Kumar, P. J. Nagtilak and M. Kapur, *New J. Chem.*, 2021, **45**, 13692–13746.
- 5 (a) C.-H. Ma, M. Chen, Z.-W. Feng, Y. Zhang, J. Wang, Y.-Q. Jiang and B. Yu, *New J. Chem.*, 2021, **45**, 9302–9314; (b) J. A. Tali, G. Kumar, B. K. Sharma, Y. Rasool, Y. Sharma and R. Shankar, *Org. Biomol. Chem.*, 2023, **21**, 7267–7289; (c) A. K. Bagdi, S. Santra, K. Monir and A. Hajra, *Chem. Commun.*, 2015, **51**, 1555–1575.
- 6 M.-S. Tang, H.-T. Wang, Y. Hu, W.-S. Chen, M. Akao, Z. Feng and W. Hu, *Mol. Nutr. Food Res.*, 2011, **55**, 1291–1300.
- 7 L. Chen, Q. Lv, J. Cai, J. Liang, Z. Liang, J. Lin, Y. Xiao, R. Chen, Z. Zhang, Y. Hong and H. Ji, *Front. Pharmacol.*, 2023, **14**, 1141121.
- 8 (a) J. T. Zacharia, T. Tanaka and M. Hayashi, *J. Org. Chem.*, 2010, **75**, 7514–7518; (b) V. K. A. Kalalbandi, J. Seetharamappa and U. Katrahalli, *RSC Adv.*, 2015, **5**, 38748–38759.
- 9 A. R. Pradipa and K. Tanaka, *Chem. Rec.*, 2021, **21**, 646–662.
- 10 R. K. Saunthwal, M. Patel, S. Kumar, A. K. Danodia and A. K. Verma, *Chem. – Eur. J.*, 2015, **21**, 18601–18605.
- 11 H. Zheng, P. He, Y. Liu, Y. Zhang, X. Liu, L. Lin and X. Feng, *Chem. Commun.*, 2014, **50**, 8794–8796.
- 12 M. Šiša, D. Pla, M. Altuna, A. Francesch, C. Cuevas, F. Albericio and M. Álvarez, *J. Med. Chem.*, 2009, **52**, 6217–6223.
- 13 A. M. Kearney and C. D. Vanderwal, *Angew. Chem., Int. Ed.*, 2006, **45**, 7803–7806.
- 14 S.-K. Xiang, B. Zhang, L.-H. Zhang, Y. Cui and N. Jiao, *Chem. Commun.*, 2011, **47**, 8097–8099.