ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2025, **61**, 19869

Received 20th September 2025,
Accepted 14th November 2025

DOI: 10.1039/d5cc05419b

rsc.li/chemcomm

Vinyl benzotriazole to indole: an iodine-mediated denitrogenative transannulation approach for the synthesis of indoles

Deepika Thakur,†[a] Shivam A. Meena,†[a] Manvi Sharma,[a] Abhijit Nandy,[b] Kirti Arora,[a] Shibdas Banerjee*[b] and Akhilesh K. Verma *[a]

A novel, convenient, and molecular iodine-mediated approach for the synthesis of 3-sulfonylated indoles from vinyl benzotriazoles is described. The reaction proceeds *via* tosylation, denitrogenative ring opening, and cyclization, featuring the cleavage of C–N and N–N bonds and the concomitant formation of C–S, N–H, and C–C bonds. This operationally simple protocol utilizes environmentally benign iodine for ring-opening reaction and circumvents the need for the protection of benzotriazoles with strong electron-withdrawing groups, metal catalysts, elevated temperatures, and extended reaction times. The mechanism is well supported by online real-time mass monitoring analysis and control experiments.

The synthesis of indole derivatives has long been a fundamental focus driven by their extensive applications in the field of drug design, agrochemicals, and alkaloids.[1–3] The 3-sulfonyl indole derivatives L-737, 126 serve as potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), whereas 5-HT6 is utilized in the treatment of CNS disorders and Alzheimer's disease (Fig. 1).[4–6] Indisulam displays inhibitory effects on carbonic anhydrases and cytosolic malate dehydrogenase.[7] Given their significance, several strategies have been devised for the construction of sulfonylated indoles over the years.[8]

Benzotriazoles have been extensively used as synthetic auxiliaries in organic reactions.[9] However, in the last few decades, benzotriazole has emerged as a versatile synthon to access heterocyclic compounds *via* ring-opening reactions.[9,10] These reactions include Dimroth-type cyclizations and Graebe-Ullmann-type reactions or pyrolysis at 600 °C (Scheme 1A(i)).[11] Despite their efficiencies, these reactions are limited by poor selectivity, competing intramolecular reactions, and the formation of multiple side products.[12] In addition, the flash vacuum pyrolysis protocol requires extremely high temperatures (500–1000 °C) under continuous vacuum and low pressure (10^{-2} Torr), resulting in significant energy and resource consumption.[13a–c]

Notably, the literature reveals a limited number of examples addressing the synthesis of heterocycles primarily from vinyl benzotriazole. Tiwari and co-workers have proficiently employed the benzotriazole ring cleavage approach for the two-step synthesis of phenanthridine from 1-(2-bromo-1-phenylethyl)-1*H*-benzotriazole (Scheme 1A(ii)).[14] Remarkably, Shi's group reported that vinyl benzotriazole reacts with $TMSN_3$ to form quinoxaline, whereas in the presence of CAN, it yields α-substituted ketones through benzotriazole elimination without ring opening (Scheme 1A(iii)).[15] Inspired by previous works and our ongoing investigation on benzotriazole chemistry and indole synthesis,[16,17] we hypothesized that the sulfonyl radical could trigger benzotriazole ring opening with subsequent cyclization, giving divergent outcomes. We herein report an unprecedented iodine-mediated ring-opening/cyclization of vinyl benzotriazole, enabling the efficient synthesis of 3-(arylsulfonyl)-1*H*-indoles (Scheme 1B).

We started our investigation with 1-(1-phenylvinyl)-1*H*-benzo[*d*][1,2,3]triazole **1a** and sodium 4-methylbenzene sulfinate **2a** as the model substrates (Table 1). When the reaction of **1a** and **2a** was carried out in the presence of I_2 and DBU with MeOH as a solvent, no product **3a** was observed (Table 1, entry 1). When the reaction was conducted in K_3PO_4 and Cs_2CO_3, product **3a** was observed in 23 and 68% yield (entries 2 and 3). Gratifyingly, the use of K_2CO_3 as a base significantly improved the yield of **3a** to 72% (entry 4). CH_3CN proved to be the optimal solvent, delivering product **3a** in

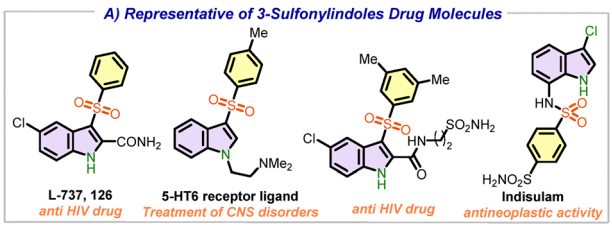
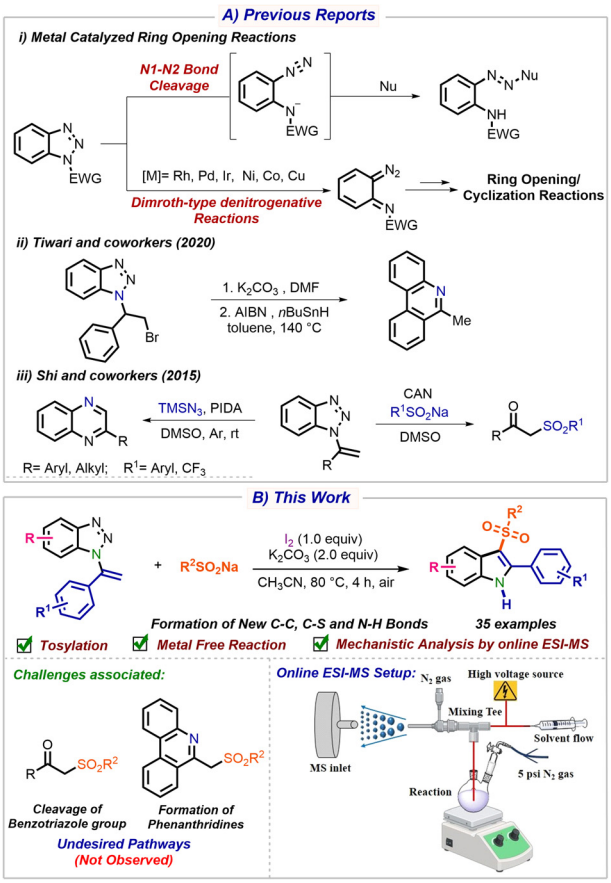


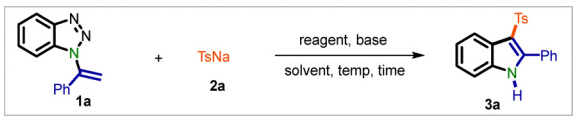
Fig. 1 3-Sulfonyl indole drug molecules.

[a] *Department of Chemistry, University of Delhi, Delhi-110007, India. E-mail: averma@acbr.du.ac.in*
[b] *Department of Chemistry, IISER Tirupati, Tirupati-517507, India*
† These authors contributed equally to this work.



Scheme 1 (A) Background work. (B) Our work.

Table 1 Optimization of the reaction conditions[a]



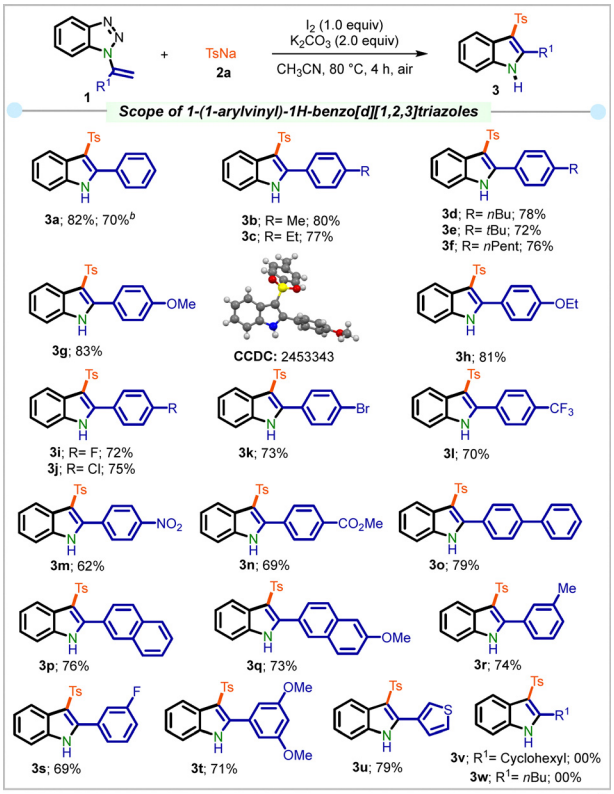
Entry	Reagent	Solvent	Base	Temp/time (°C h^{-1})	Yield[b] (%)
1	I_2	MeOH	DBU	80/4	00
2	I_2	MeOH	K_3PO_4	80/4	23
3	I_2	MeOH	Cs_2CO_3	80/4	68
4	I_2	MeOH	K_2CO_3	80/4	72
5	I_2	CH_3CN	K_2CO_3	80/4	82
6	I_2	CH_3CN	K_2CO_3	80/4	64[c],52[d]
7	I_2	CH_3CN	K_2CO_3	80/2	55, 81[e]
8	I_2	CH_3CN	K_2CO_3	25/6	30
9	I_2	CH_3CN	K_2CO_3	60/6	46, 65[e]
10	NIS	CH_3CN	K_2CO_3	80/6	16, 0[f]
11	—	CH_3CN	K_2CO_3	80/6	n.r.
12	I_2	CH_3CN	K_2CO_3	80/4	80[g], 77[h]

[a] Reactions were performed using 0.23 mmol of **1a**, 1.2 equiv. of **2a**, 1.0 equiv. of reagent, and 2.0 equiv. of base in 3.0 mL solvent. [b] Isolated yields. [c] 1.0 equiv. of **2a** was used. [d] Using 0.5 equiv. of I_2. [e] 12 h. [f] PIDA was used instead of NIS. [g] N_2. [h] Ar.

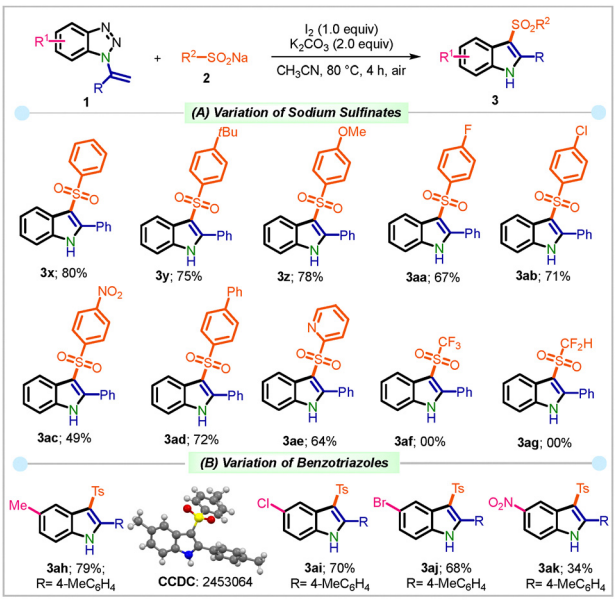
82% yield (entry 5). Decreasing the loading of **2a** and I_2 led to 64 and 52% yield of product **3a** (entry 6). Notably, decreasing or extending the reaction duration did not enhance the reaction yield (entry 7). Performing the reaction at 25 and 60 °C led to 30–65% yield of product **3a** (entries 8 and 9). Use of other iodine sources, such as NIS and PIDA, was found to be inferior for the reaction (entry 10). No product **3a** was obtained in the absence of I_2, confirming its essential role in radical generation (entry 11). Performing the reaction under an inert atmosphere (N_2 or Ar) afforded product **3a** in comparable yields, indicating that the atmosphere has little effect on the reaction outcome (entry 12).

Having established the optimal conditions, the scope of this protocol was investigated using a variety of 1-(1-arylvinyl)-1*H*-benzo[*d*][1,2,3]triazoles **1** (Scheme 2). The reactions of vinyltriazoles **1** bearing methyl (**1b**), ethyl (**1c**), *n*-butyl (**1d**), *t*-butyl (**1e**), and *n*-pentyl (**1f**) groups at the *p*-position of the phenyl ring gave the products **3b–3f** in 72–80% yields. When a scale-up reaction was performed using 4.52 mmol of **1a**, product **3a** was obtained in 70% yield. Likewise, *p*-methoxy and *p*-ethoxyvinyltriazole (**1g–h**) furnished the products **3g** and **3h** in 83 and 81% yield. Substrates **1i–1k** bearing halogens at the *p*-position of the phenyl group provided **3i–3k** in 72–75% yield. Notably, electron-withdrawing groups such as $-CF_3$, $-NO_2$, and $-CO_2Me$ gave the corresponding products **3l–n** in 62–70% yield.

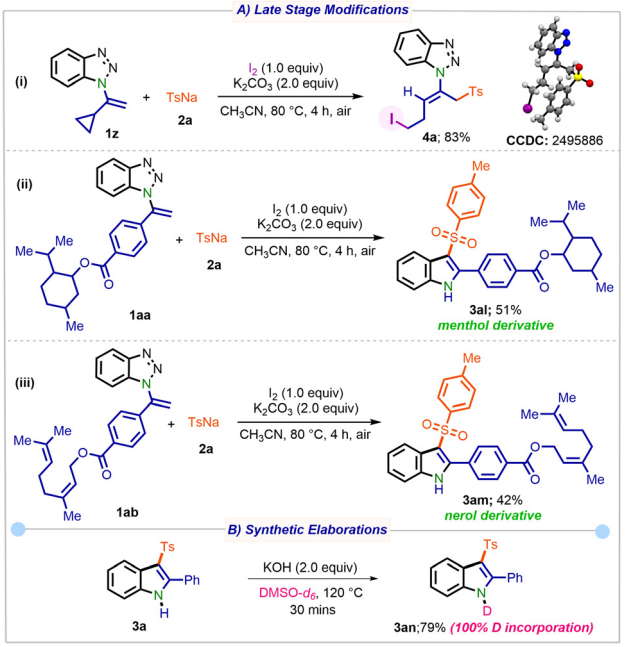
The 1,1′-biphenyl and naphthyl-tethered benzotriazole **1o–q** were amenable in this transformation, delivering **3o–q** in 73–79% yield. Similar results were obtained with *meta*-substituted substrates having methyl (**1r**) and fluoro (**1s**) groups, which led to the product **3r–s** in 69–74% yield. The developed protocol



Scheme 2 Substrate scope of the vinyl benzotriazoles (R^1): reactions were performed using 0.23 mmol of **1a**, 1.2 equiv. of **2a**, 1.0 equiv. of I_2, and 2.0 equiv. of K_2CO_3 in 3.0 mL solvent CH_3CN at 80 °C for 4 h in air. [b] Gram scale synthesis using 4.52 mmol of **1a**.



Scheme 3 (A) Scope of sodium sulfinates (R^2). (B) Scope of benzotriazoles (R^1). Reactions were performed using 0.23 mmol of **1a**, 1.2 equiv. of **2a**, 1.0 equiv. of I_2, and 2.0 equiv. of K_2CO_3 in 3.0 mL solvent CH_3CN at 80 °C for 4 h in air.



Scheme 4 (A) Late-stage modifications. (B) Synthetic elaboration.

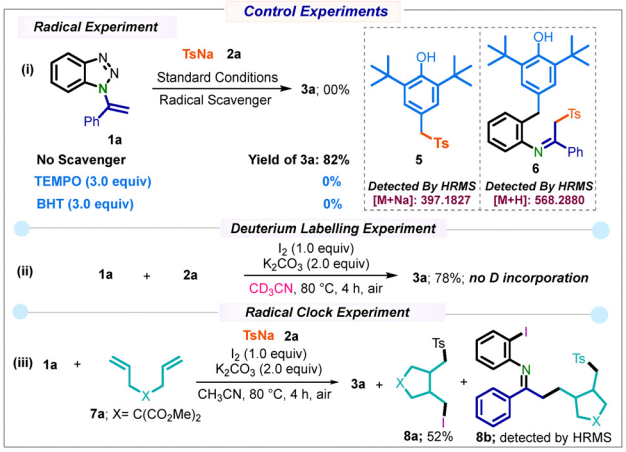
furnished di-substituted product **3t** bearing a 2,5-dimethoxy group, and **3u** bearing a 3-thienyl group in 71 and 79% yield, respectively. However, substrates **1v–w** bearing aliphatic substituents at the R^1 position failed to afford the desired products **3v** and **3w**.

We next extended the developed protocol to a range of sodium sulfinate salts **2** (R^2) (Scheme 3A). Arylsulfinates bearing –H, –*t*Bu, and –OMe were found suitable, providing products **3x–z** in 75–80% yields. Electron-withdrawing groups such as fluoro, chloro, and nitro at the *p*-position of the sulfinate derivatives furnished **3aa–ac** in 49–71% yield. Furthermore, sodium [1,1′-biphenyl]-4-sulfinate **2h** and heterocyclic sodium pyridine-3-sulfinate **2i** led to product **3ad–ae** in good yields. However, the aliphatic sulfinate salt **2j–k** failed to deliver the desired product **3af–ag** under the standard reactions conditions. Next, the substrate scope for different benzotriazoles (R^1) was evaluated. Introduction of different groups at the 5-position of vinyl benzotriazole (**1v**) led to **3ah–ak** in 34–79% yield (Scheme 3B).

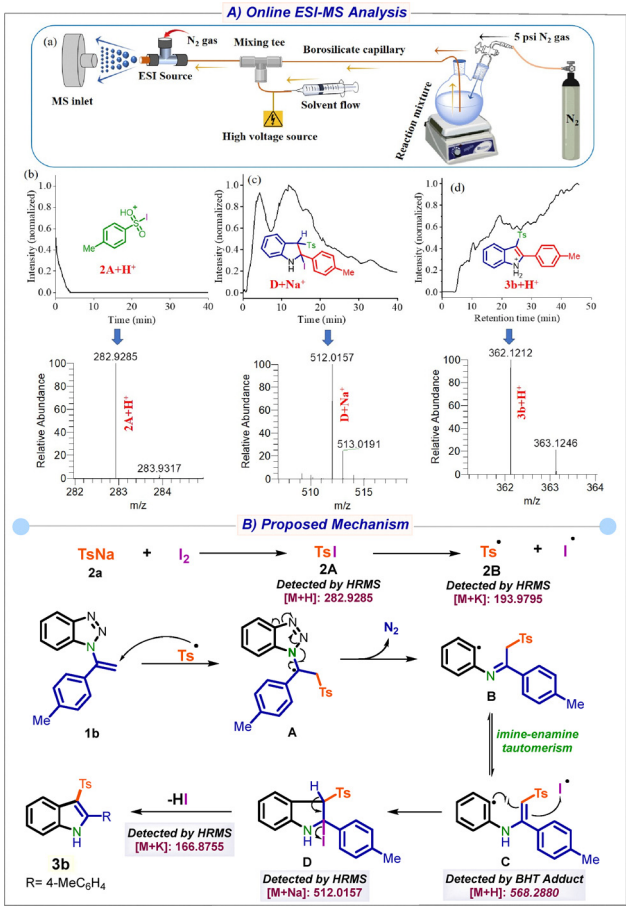
Interestingly, when **1z** was subjected to the reaction conditions, ring opening occurred preferentially at the cyclopropyl moiety rather than the benzotriazole, furnishing the sole *E*-iodo substituted product **4a** in 83% yield (Scheme 4A(i)). The applicability of the developed protocol was further showcased through late-stage modifications. Sulfonylated analogues **3al** and **3am**, derived from menthol and nerol, were obtained in 51 and 42% yield, respectively. When **3a** was treated with KOH in DMSO-d_6, product **3an** was obtained in 79% yield with 100% deuterium incorporation on the nitrogen centre (Scheme 4B).

To rationalize the mechanistic pathway, several control experiments were conducted (Scheme 5). The addition of radical scavengers such as TEMPO and BHT to the reaction mixture effectively inhibited the product formation, proving that the transformation initiates *via* radical reaction (Scheme 5(i)). Also, BHT adduct **5** was detected by HRMS, confirming the *in situ* generation of tosyl radicals. Meanwhile, the detection of another BHT adduct **6** supports the formation of radical species **B**. A deuterium-labelling experiment in CD_3CN showed no *D*-incorporation (Scheme 5(ii)), suggesting that the solvent does not serve as a proton source. A radical clock experiment with substrate **7a** afforded product **8a** in 52% yield along with the ring-opened product **8b** (detected by HRMS), supporting a radical ring-opening mechanism.

To further support the mechanism, online ESI-MS analysis for real-time detection of reactive intermediates was conducted (Scheme 6A). Online ESI-MS analysis plots confirm the formation of tosyl iodide **2A**, which decreases with time, showing the consumption of intermediates (for more details, see the SI,



Scheme 5 Control experiments.



Scheme 6 (A) Custom-built online ESI-MS setup and real-time mass monitoring of the reaction. (B) Proposed reaction mechanism.

Fig. S4). The tosyl radical **2B** is also detected by online ESI-MS analysis, and BHT trapping confirms that the reaction initiates *via* a radical pathway. The online ESI-MS analysis also confirms the formation of iodo-substituted indoline species **D**, which converts into product **3b**. Based on these findings from control experiments, online ESI-MS analysis, and previous reports,[15,16,18] a plausible mechanism is proposed in Scheme 6B. The reaction begins with the formation of tosyl iodide **2A** from sodium sulfinate **2a** and I_2. The thermal homolytic cleavage of tosyl iodide **2A** results in the formation of tosyl radical **2B** (detected by online ESI-MS and BHT) and an iodine radical. The tosyl radical attacks vinyl benzotriazole **1b**, which generates species **A**. Then, species **A** undergoes a ring-opening reaction by the release of N_2 gas, generating species **B**. This species further undergoes rapid tautomerisation to generate **C**. The radical at the phenyl ring attacks the alkene, which in turn attacks the iodine radical, generating 2-iodo-2-(*p*-tolyl)-3-tosylindoline **D** (captured by real-time mass monitoring), which finally, by the elimination of HI, led to 3-tosyl indole **3b**.

In conclusion, we have developed a metal-free iodine-mediated ring opening of vinyl benzotriazoles for the synthesis of 3-sulfonyl indoles bearing a free N–H group. This operationally simple method features high functional group tolerance, which renders the late-stage functionalization of relevant molecules such as menthol and nerol. The success of this reaction is attributed to a radical pathway, supported by mechanistic investigations including real-time mass monitoring studies, which involves tosyl iodide-mediated benzotriazole ring opening, N_2 extrusion, and subsequent cyclization.

This work was supported by SERB (CRG/2022/008887). D. T. and S. A. M. thank CSIR for SRF fellowships and acknowledge the University of Delhi and USIC for instrumentation support.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study including ^{1}H-NMR, ^{13}C-NMR, SC-XRD and HRMS of all the synthesized compounds are available in the published article and its supplementary information (SI). See DOI: **https://doi.org/10.1039/d5cc05419b**.

CCDC 2453343, 2453064 and 2495886 contain the supplementary crystallographic data for this paper.[19a–c]

Notes and references

1 (*a*) T. V. Sravanthi and S. L. Manju, *Eur. J. Med. Chem.*, 2016, **124**, 74; (*b*) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, **18**, 6620.
2 P. Sun, Y. Huang, S. Chen, X. Ma, Z. Yang and J. Wu, *Chin. Chem. Lett.*, 2024, **35**, 109005.
3 A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489.
4 F. Zhao, W. Hagui, M. Ballarín-Marión, C. Ollivier, V. Mouriès-Mansuy and L. Fensterbank, *ACS Org. Inorg. Au*, 2022, **3**, 19.
5 F. Piscitelli, A. Coluccia, A. Brancale, G. La Regina, A. Sansone, C. Giordano, A. Samuele, R. Cirilli, F. La Torre, A. Lavecchia, E. Novellino and R. Silvestri, *J. Med. Chem.*, 2009, **52**, 1922.
6 (*a*) R. Bernotas, S. Lenicek, S. Antane, G. M. Zhang, D. Smith, J. Coupet, B. Harrison and L. E. Schechter, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5499; (*b*) R. C. Bernotas, S. Antane, R. Shenoy, V.-D. Le, B. L. Harrison, A. J. Robichaud, G. M. Zhang, D. Smith and L. E. Schechter, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1657.
7 C. T. Supuran, *Expert Opin. Investig. Drugs*, 2003, **12**, 283.
8 (*a*) J. K. Qiu, W. J. Hao, D. C. Wang, P. Wei, J. Sun, B. Jiang and S. J. Tu, *Chem. Commun.*, 2014, **50**, 14782; (*b*) D. Xia, L. Jiang, Y. Li and J. Kong, *Org. Biomol. Chem.*, 2024, **22**, 5511; (*c*) N. Chakraborty, A. Dahiya, A. Rakshit, A. Modi and B. K. Patel, *Org. Biomol. Chem.*, 2021, **19**, 6847.
9 (*a*) A. R. Katritzky, X. Lan and J. N. Lam, *J. Org. Chem.*, 1991, **56**, 4397; (*b*) A. R. Katritzky and S. Rachwal, *Chem. Rev.*, 2010, **110**, 1564.
10 For Selected Reviews: (*a*) M. Akter, K. Rupa and P. Anbarasan, *Chem. Rev.*, 2022, **122**, 13108; (*b*) Y. Wang, Z. Wang and Y. Tang, *Chem. Rec.*, 2020, **20**, 693.
11 (*a*) O. Dimroth, *Justus Liebigs Ann. Chem.*, 1909, **364**, 183–226; (*b*) S. J. Barker and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 1990, 485; (*c*) P. Vera-Luque, R. Alajarín, J. Alvarez-Builla and J. J. Vaquero, *Org. Lett.*, 2006, **8**, 415.
12 I. Nakamura, T. Nemoto, N. Shiraiwa and M. Terada, *Org. Lett.*, 2009, **11**, 1055.
13 (*a*) M. Teders, L. Pitzer, S. Buss and F. Glorius, *ACS Catal.*, 2017, **7**, 4053; (*b*) V. Helan, A. V. Gulevich and V. Gevorgyan, *Chem. Sci.*, 2015, **6**, 1928; (*c*) S. W. Kwok, L. Zhang, N. P. Grimster and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2014, **53**, 3452.
14 (*a*) M. S. Yadav, A. S. Singh, A. K. Agrahari, N. Mishra and V. K. Tiwari, *ACS Omega*, 2019, **4**, 6681; (*b*) M. Singh, P. Bose, A. S. Singh and V. K. Tiwari, *Tetrahedron*, 2020, **76**, 131078.

15 Y. Su, J. L. Petersen, T. L. Gregg and X. Shi, *Org. Lett.*, 2015, **17**, 1208.
16 J. Li, S. Wang, J. Zhao and P. Li, *Org. Lett.*, 2022, **24**, 5977.
17 (*a*) M. Sharma, D. Thakur and A. K. Verma, *Chem. Commun.*, 2024, **60**, 12840; (*b*) A. K. Verma, T. Kesharwani, J. Singh and R. C. Larock, *Angew. Chem., Int. Ed.*, 2009, **48**, 1158; (*c*) A. K. Verma, J. Singh and R. C. Larock, *Tetrahedron*, 2009, **65**, 8434; (*d*) D. Thakur, S. A. Meena, M. Sharma and A. K. Verma, *Chem. Commun.*, 2025, **61**, 5313; (*e*) S. A. Meena, D. Thakur, R. Ranjan and A. K. Verma, *Chem. Commun.*, 2024, **60**, 9230.
18 (*a*) H. Long, K. Xu, S. Chen, J. Lin, D. Wu, B. Wu, X. Tian and L. Ackermann, *Org. Lett.*, 2019, **21**, 3053; (*b*) A. K. Sahoo, A. Dahiya, B. Das, A. Behera and B. K. Patel, *J. Org. Chem.*, 2021, **86**, 11968.
19 (*a*) CCDC 2453343: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2nbx31**; (*b*) CCDC 2453064: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2nbm3r**; (*c*) CCDC 2495886: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2ps5g4**.