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Brønsted acid-mediated mono- and di-substitution of quinoxalines with indoles: a pathway to indolocarbazole-quinoxaline scaffolds†

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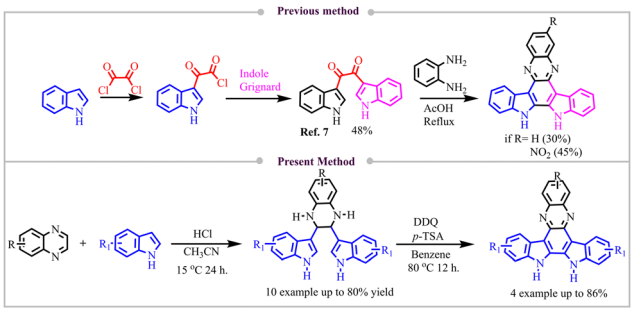
A versatile and efficient protocol for the mono- and di-substitution of quinoxalines with indoles has been developed, offering a direct pathway to indolocarbazole-quinoxaline scaffolds. By optimizing the reaction conditions, selective coupling at the C-2 and C-3 positions of quinoxalines with diverse indole derivatives was achieved under transition metal-free conditions. Substrate scope evaluation revealed broad functional group tolerance and the synthetic utility was demonstrated by gram-scale synthesis and subsequent cyclization into novel indolocarbazole-quinoxalines. Mechanistic studies suggest an ionic pathway, highlighting the potential of this method for constructing biologically relevant heterocyclic architectures.

Alkaloids are naturally occurring nitrogen-containing organic compounds found in diverse sources, including plants, fungi, animals, insects, marine organisms, and microorganisms.[1] These compounds are vital in modern medicinal applications, exhibiting diverse therapeutic properties. Among them, indolocarbazoles form an important class of alkaloids with a broad spectrum of biological activities, such as antimicrobial, anti-HIV, anticancer, protein kinase C inhibition, and antitumor effects.[2] Staurosporine, the first indolocarbazole family member to be successfully isolated, was obtained from *Streptomyces staurosporeus* in 1977 and demonstrated potent hypotensive and antimicrobial properties.[3] Since then, extensive research has been focused on the synthesis of indolocarbazoles and explored their potential as drug candidates.[4] Indolocarbazole-quinoxalines (ICQs) are a subclass of indolocarbazoles where the indole and quinoxaline units are connected through a fused ring system, typically forming a carbazole scaffold. These molecules act as synthetic receptors and chemosensors for anion recognition,[5] which are critical in numerous chemical, biological, and environmental processes.[6] The Yan group reported the synthesis of ICQs in 2008, and highlighted their efficiency in sensing acetate and fluoride anions.[7] They initiated their reaction with indole and 2-(3-indolyl)-2-oxoacetyl chloride, to synthesize diindolylquinoxalines (DIQs) by following a previously reported procedure.[8] The synthesis of the final ICQs involved a three-step reaction and purification process, which rendered the method both time-consuming and cost-inefficient.

In continuation of our efforts on the development of novel and efficient methods for the synthesis and functionalization of N-heterocycles,[9] herein we report a Brønsted acid-mediated approach for the synthesis of biologically active indolocarbazole-quinoxaline scaffolds through the coupling of quinoxalines with indole derivatives. This method reduces the reaction to two steps, offering an improved yield and greater efficiency in the construction of these important molecules (Scheme 1).

We initiated our studies by investigating the reaction of quinoxaline (**1a**) and indole (**2a**) under various conditions to optimize the synthesis of the desired products, as summarized in Table 1. Using HCl (1.2 equiv.) as a mediator in CH_3CN at 70 °C for 24 hours, the desired product, 2-(1*H*-indol-3-yl)quinoxaline (**3aa**), was isolated in 65% yield. We tested different acids and observed comparatively



Scheme 1 Synthesis of indolocarbazole-quinoxaline.

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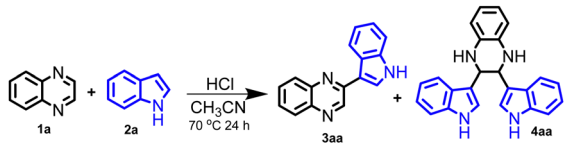
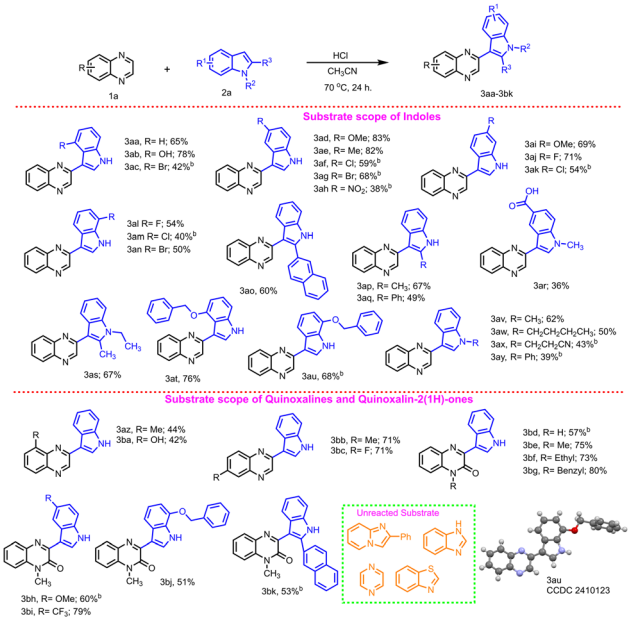
† Electronic supplementary information (ESI) available. CCDC 2410123 and 2408003. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4cc06606e

Table 1 Optimization of the conditions[a]



Entry	Deviations from standard conditions	Yield (%) 3aa	4aa[b]
1	No deviations	65	—
2	H_2SO_4	42	—
3	HBr	53	—
4	$AlCl_3$	nr	nr
5	15 °C and 2.0 equiv. **2a**	—	66
6	H_2SO_4, 15 °C and 2.0 equiv. **2a**	—	53
7	HBr, 15 °C and 2.0 equiv. **2a**	Trace	30
8	0 °C and 2.0 equiv. **2a**	Trace	47
9	10 °C and 2.0 equiv. **2a**	Trace	48
10	20 °C and 2.0 equiv. **2a**	5	41
11	rt and 2.0 equiv. **2a**	49	31
12	50 °C and 2.0 equiv. **2a**	50	Trace
13	100 °C and 2.0 equiv. **2a**	59	—

[a] Reaction conditions: quinoxaline (**1a**) (0.3 mmol), indole (**2a**) (1 equiv.) and HCl (1.2 equiv.) in solvent at 70 °C, isolated yield w.r.t. **1a**. [b] 2.0 equiv. HCl was used.



Scheme 2 Substrate scope of mono-substitution.[a a] Reaction conditions: 1**a** (0.3 mmol), **2a** (1 equiv.), and HCl (1.2 equiv.) in acetonitrile at 70 °C for 24 h, isolated yield. [b]The reaction temp. is 80 °C and time 48 h.

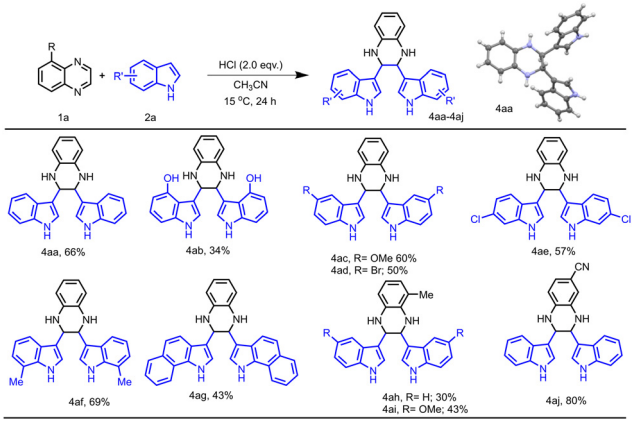
lower yields of product **3aa**. In H_2SO_4 and HBr, we obtained 42% and 53% yields of **3aa**, respectively, while with $AlCl_3$, no reaction was observed (Table 1, entries 2–4). Lowering the temperature to 15 °C and increasing HCl and indole to 2.0 equivalents each led to the formation of 2,3-di(1*H*-indol-3-yl)quinoxaline (**4aa**) with a 66% isolated yield, while **3aa** was not formed under these conditions (Table 1, entry 5). We then explored alternative acids. Both H_2SO_4 and HBr provided lower yields of product **4aa**. In H_2SO_4, no formation of **3aa** was observed, while in HBr, only traces of **3aa** were detected (Table 1, entries 6 and 7). Temperature variations significantly impacted the product distribution. At 0 °C, no formation of **3aa** was observed, while **4aa** was obtained in 47% yield (Table 1, entry 8). At 10 °C, traces of **3aa** and a 48% yield of **4aa** were observed (Table 1, entry 9). Increasing the temperature to 20 °C resulted in a 5% yield of **3aa** and a 41% yield of **4aa** (Table 1, entry 10). At room temperature, the reaction produced 49% of **3aa** and 31% of **4aa** (Table 1, entry 11). At 50 °C, **3aa** was formed in 50% yield, with only trace amounts of **4aa** detected (Table 1, entry 12). At 100 °C, the reaction yielded 59% of **3aa**, but no formation of **4aa** was observed (Table 1, entry 13). By adjusting the reaction temperature, the selectivity between products **3aa** and **4aa** could be effectively controlled. Detailed optimization studies showcasing the impact of solvent, temperature, catalyst, and reagents are available in the ESI† (see ESI,† for details).

With the optimized reaction conditions established (Table 1 entry 1), we explored the substrate scope of quinoxaline and indole derivatives, as summarized in Scheme 2. Starting with indoles, we investigated substitutions at different positions. At the C-4 position, indoles bearing H, OH, and Br substitutions yielded the products **3aa**–**3ac** in moderate to good yields (42–78%). Substituents at the C-5 position of indoles, whether electron-donating or electron-withdrawing, also resulted in good yields (59–83%) of products (**3ad**–**3ag**), while the nitro group significantly lowered the product (**3ah**) yield to 38%. Indoles substituted at the C-6 position with –OMe, –F, or –Cl gave the corresponding products **3ai**–**3ak** in yields ranging from 54% to 71%. Similarly, C-7-substituted indoles with fluoro, chloro, or bromo groups provided the products **3al**–**3an** in 54%, 40%, and 50% yields, respectively. Indoles having naphthalene, methyl, and phenyl substituents at the C-2 position also produced the products **3ao**–**3aq** in 60%, 67%, and 49% yields, respectively. Di-substituted indoles, such as 1-methyl-1*H*-indole-5-carboxylic acid and 1-ethyl-2-methyl-1*H*-indole, yielded **3ar** and **3as** in 36% and 67% yields, respectively. Benzyloxy substitutions at the C-4 and C-7 positions afforded the products **3at** and **3au** in 76% and 68% yields. The structure of product **3au** was further validated by single-crystal XRD analysis (CCDC 2410123†). Substituents at the N1 position of indole, including methyl, butyl, propionitrile and phenyl, provided the products **3av**–**3ay** in moderate yields (39–62%). Moving to quinoxaline derivatives, which have methyl and hydroxy groups at the C-5 position provided the products **3az** and **3ba** in 44% and 42% yields. Quinoxalines having methyl, and fluoro, substituents at the C-6 position, produced the products **3bb** and **3bc** in 71% yields in each case. We further extended the same reaction conditions to quinoxaline-2(1*H*)-one (**1b**), and obtained the C-3 indole-coupled product **3bd** in 57% yield. Recognizing the importance of C-3-hetero-substituted quinoxaline-2(1*H*)-ones,[10] we examined the derivatives of quinoxaline-2(1*H*)-ones with $N-1$ substituents such as methyl, ethyl, and benzyl. These derivatives provided the desired products **3be**–**3bg** in good to excellent yields (73–80%). Substituted indoles with 1-methylquinoxaline-2(1*H*)-one (**3c**) were also tested. Methoxy (−OMe) and trifluoromethyl ($-CF_3$)

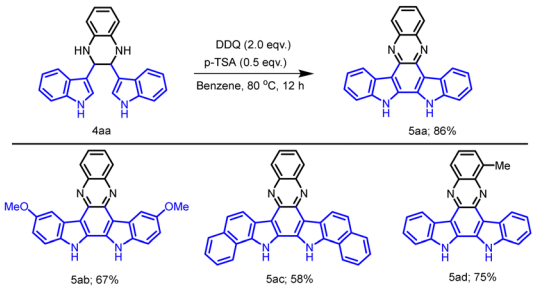
groups at the C-5 position of indole gave the corresponding products **3bh** and **3bi** in 60% and 79% yields. Benzyloxy substitution at C-7 and naphthalene at the C-2 position of indoles afforded **3bj** and **3bk** in 51% and 53% yields, respectively. Finally, we attempted to extend the reaction conditions to other N-heterocycles, including 2-phenylimidazo[1,2-*a*] pyridine, 1*H*-benzo[*d*]imidazole, pyrazine, and benzo[*d*]thiazole; unfortunately, these substrates were unsuccessful, highlighting the specificity of the reaction conditions.

Building on our optimized conditions (Table 1, entry 1), we proceeded to synthesize diindolylquinoxaline derivatives, as shown in Scheme 3. Quinoxaline reacted with indole to yield the disubstituted product **4aa** in 66% yield. Under these conditions, to show the efficacy of the method, a few representative examples were presented (Scheme 3). Indoles having substituent groups (hydroxy, methoxy, bromo, chloro and methyl) at the C-4, C-5, C-6 and C-7 positions, reacted well and provided the corresponding products **4ab**–**4af** in moderate to good yields (34–69%). One of the products **4aa** has been further confirmed through single crystal XRD analysis (CCDC 2408003†). Extending the conditions to 1*H*-benzo[*g*]indole produced the product **4ag** in 43% yield. We also explored the substituted quinoxalines. A 5-methylquinoxaline derivative reacted with indole to produce **4ah** in 30% yield, while coupling with 5-methoxyindole yielded the desired product **4ai** in 43% yield. Quinoxaline with electron-withdrawing substituents also performed well in this transformation, yielding the corresponding product **4aj** in 80% yield.

After successfully establishing the substrate scope, we explored the synthetic utility of this methodology by aiming to cyclize diindolylquinoxaline derivatives into indolocarbazole-quinoxalines. Starting with 2,3-di(1*H*-indol-3-yl)-1,2,3,4-tetrahydroquinoxaline (**4aa**), we optimized the various parameters, including catalysts, oxidants, solvents, reaction time, and temperature (for details see Tables S4–S6 in the ESI†). Using 2.0 equivalents of DDQ as an oxidant, and 50 mol% *p*-TSA as a mediator, in benzene as the solvent at 80 °C, we obtained 86% isolated yield of the desired product 5,6-dihydrodiindolo[3,2-*a*:2′,3′-*c*] phenazine (**5aa**) in 12 hours (Scheme 4). Furthermore, the cyclization of other



Scheme 3 Substrate scope of di-substitution.[a] [a]Reaction conditions: **1a** (0.3 mmol), **2a** (2.0 equiv.), and HCl (2 equiv.) in acetonitrile at 15 °C for 24 h, isolated yield.



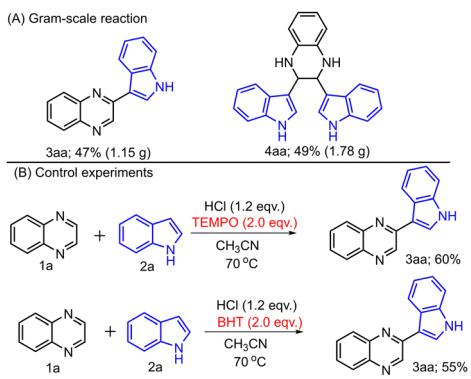
Scheme 4 Substrate scope of indolocarbazole-quinoxalines.[a] [a]Reaction conditions: **4aa** (0.1 mmol), DDQ (2 equiv.), *p*-TSA (0.5 equiv.) in benzene at 80 °C for 12 h, isolated yield.

derivatives with substitutions on both indole as well as quinoxaline provided the desired products **5ab**–**5ad** in good yields (58–75%) demonstrating the versatility of the reaction conditions. To evaluate the practical utility of this protocol, we scaled up the synthesis of both the mono-substituted product (**3aa**) and the disubstituted product (**4aa**) to gram-scale quantities. The reactions yielded 47% and 37%, respectively, as shown in Scheme 5A.

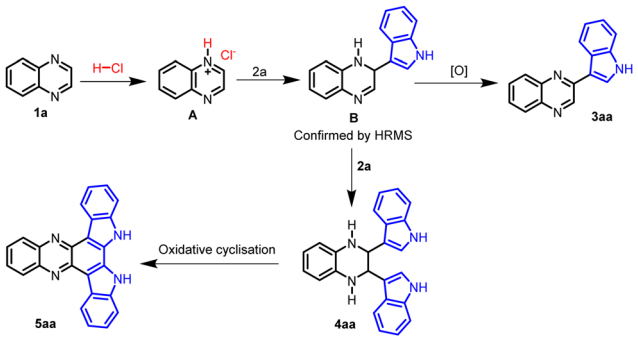
To gain insight into the reaction mechanism, we carried out control experiments (Scheme 5B). The use of radical scavengers such as TEMPO and BHT slightly affected the reaction outcome, resulting in 60% and 55% yields of **3aa**, respectively. This suggests that the reaction likely proceeds through an ionic pathway rather than a radical one.

Based on control experiments and literature reports,[11] we proposed a plausible reaction mechanism (Scheme 6). In the presence of HCl, compound **1a** forms an intermediate **A**. A nucleophilic attack by **2a** on **A** leads to the formation of intermediate **B**, which is confirmed by HRMS analysis (see Fig S2 under ESI†). Upon oxidation of intermediate **B**, the desired product **3aa** was produced. At low temperatures, an additional molecule of **2a** reacts with intermediate **B**, resulting in the formation of 2,3-di(1*H*-indol-3-yl)-1,2,3,4-tetrahydroquinoxaline (**4aa**) as the final product. Furthermore, product **4aa** can be readily converted into the cyclized product **5aa** through oxidative cyclization.

This study provides a practical and scalable method for synthesizing mono- and di-indole-substituted quinoxalines and



Scheme 5 (A) Gram-scale synthesis and (B) control experiments.



Scheme 6 Plausible reaction mechanism.

their cyclized indolocarbazole derivatives. The developed protocol exhibits high functional group compatibility, enabling the synthesis of complex heterocyclic frameworks with moderate to good yields. Gram-scale synthesis underscores the method's applicability, while mechanistic investigations confirm the ionic nature of the transformation. This work lays a foundation for further exploration of indolocarbazole-quinoxalines in medicinal and material science applications, showcasing the power of this straightforward and adaptable approach.

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Data availability

The data supporting this article have been included as part of the ESI† (NMR and HRMS spectra). Crystallographic data for the **3au** and **4aa** compounds has been deposited at the CCDC under 2410123 and 2408003 correspondingly.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) K.-T. Lee, *Nature*, 1960, **188**, 65–66; (*b*) J. Pavón-Pérez, A. Vallejos-Almirall, C. Agurto-Muñoz and O. Galarce-Bustos, *Green Chem.*, 2022, **24**, 9450–9474; (*c*) P. K. Teja, B. Q. Ly, D. K. Shah and S. K. Chauthe, *ACS Omega*, 2023, **8**, 11201–11212; (*d*) M. Gill and W. Steglich, in *Progress in the Chemistry of Organic Natural Products*, ed. W. Herz, H. Grisebach and G. W. Kirby, Springer, Wien, 1987, vol. 51, pp. 1–317; (*e*) J. Bergman, *Studies in Natural Products Chemistry, Part A*, Elsevier Science, New York, 1988, vol. 1, pp. 3–30.

2 (*a*) S. B. Bharate, S. D. Sawant, P. P. Singh and R. A. Vishwakarma, *Chem. Rev.*, 2013, **113**, 6761–6815; (*b*) G. W. Gribble and S. J. Berthel, in *Studies in Natural Products Chemistry*, ed. A. Rahman, Elsevier, New York, 1993, vol. 12, pp. 365–409; (*c*) W. Steglich, *Pure Appl. Chem.*, 1989, **61**, 281–288; (*d*) J. B. McAlpine, J. P. Karwowski, M. Jackson, M. M. Mullally, J. E. Hochlowski, U. Premachandran and N. S. Burres, *J. Antibiot.*, 1994, **47**, 281–288; (*e*) D. E. Nettleton, T. W. Doyle, B. Kirshnan, G. K. Matsumoto and J. Clardy, *Tetrahedron Lett.*, 1985, **26**, 4011–4014; (*f*) J. A. Bush, B. H. Long, J. J. Catino, W. T. Bradner and K. Tomita, *J. Antibiot.*, 1987, **40**, 668–674; (*g*) H. Nakano and S. Ōmura, *J. Antibiot.*, 2009, **62**, 17–26.

3 S. Ōmura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi and R. Asuma, *J. Antibiot.*, 1977, **30**, 275–282.

4 (*a*) G. E. Chambers, A. E. Sayan and R. C. D. Brown, *Nat. Prod. Rep.*, 2021, **38**, 1794–1820; (*b*) D. Curiel, A. Cowley and P. D. Beer, *Chem. Commun.*, 2005, 236–238; (*c*) T. Janosik, A. Rannug, U. Rannug, N. Wahlström, J. Slätt and J. Bergman, *Chem. Rev.*, 2018, **118**, 9058–9128.

5 (*a*) S. K. Dey, M. Al Kobaisi and S. V. Bhosale, *ChemistryOpen*, 2018, **7**, 934–952; (*b*) C. Suksai and T. Tuntulani, *Chem. Soc. Rev.*, 2003, **32**, 192–202.

6 (*a*) P. D. Beer, *Acc. Chem. Res.*, 1998, **31**, 71–80; (*b*) P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 486–516.

7 (*a*) T. Wang, Y. Bai, L. Ma and X.-P. Yan, *Org. Biomol. Chem.*, 2008, **6**, 1751–1755; (*b*) J. L. Sessler, D.-G. Cho and V. Lynch, *J. Am. Chem. Soc.*, 2006, **128**, 16518–16519.

8 (*a*) M. M. Krayushkin, V. N. Yarovenko and I. P. Sedishev, *et al.*, *Russ. J. Org. Chem.*, 2005, **41**, 875–883; (*b*) T. Mizuno, W.-H. Wei, L. R. Eller and J. L. Sessler, *J. Am. Chem. Soc.*, 2002, **124**, 1134–1135.

9 (*a*) A. Joshi, R. Semwal, E. Suresh and S. Adimurthy, *Chem. Commun.*, 2019, **55**, 10888–10891; (*b*) G. Badhani, A. Joshi and S. Adimurthy, *Eur. J. Org. Chem*, 2021, **48**, 6705–6716; (*c*) G. Badhani and S. Adimurthy, *Monatsh. Chem.*, 2024, **155**, 613–619; (*d*) S. Samanta, C. Ravi, S. N. Rao, A. Joshi and S. Adimurthy, *Org. Biomol. Chem.*, 2017, **15**, 9590–9594; (*e*) G. Badhani, V. M. Biramya and S. Adimurthy, *New J. Chem.*, 2023, **47**, 21596–21599; (*f*) G. Badhani and S. Adimurthy, *ChemistrySelect*, 2023, **8**, e202302159; (*g*) R. Semwal, G. Badhani and S. Adimurthy, *Chem. Commun*, 2021, **57**, 1585–1588; (*h*) G. Badhani Subham, N. V. M. Biramya and S. Adimurthy, *J. Org. Chem*, 2024, **89**(15), 10760–10772.

10 (*a*) A. Gazit, K. Yee, A. Uecker, F. D. Bohmer, T. Sjoblom, A. Ostman, J. Waltenberger, G. Golomb, S. Banai, M. C. Heinrich and A. Levitzki, *Bioorg. Med. Chem.*, 2003, **11**, 2007–2018; (*b*) M. R. Myers, W. He, B. Hanney, N. Setzer, M. P. Maguire, A. Zulli, G. Bilder, H. Galzcinski, D. Amin, S. Needle and A. P. Spada, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3091–3095; (*c*) K. Aoki, T. Obata, Y. Yamazaki, Y. Mori, H. Hirokawa, J. Koseki, T. Hattori, K. Niitsu, S. Takeda, M. Aburada and K. Miyamoto, *Chem. Pharm. Bull.*, 2007, **55**, 255–267.

11 (*a*) S. Kamila, H. Ankati and E. R. Biehl, *Arkivoc*, 2011, **9**, 94–104; (*b*) S. Uçar and A. Daştan, *J. Org. Chem.*, 2020, **85**, 15502–15513; (*c*) D. A. Gazizov, E. B. Gorbunov, E. F. Zhilina, P. A. Slepukhin and G. L. Rusinov, *J. Org. Chem.*, 2022, **87**, 13011–13022; (*d*) D. A. Gazizov, E. B. Gorbunov, E. F. Zhilina, P. A. Slepukhin and G. L. Rusinov, *J. Org. Chem.*, 2022, **87**, 13011–13022.