

Bench-Stable Electrophilic Reagents for the Direct Di- and Trifluoroethylthiolation of Indoles

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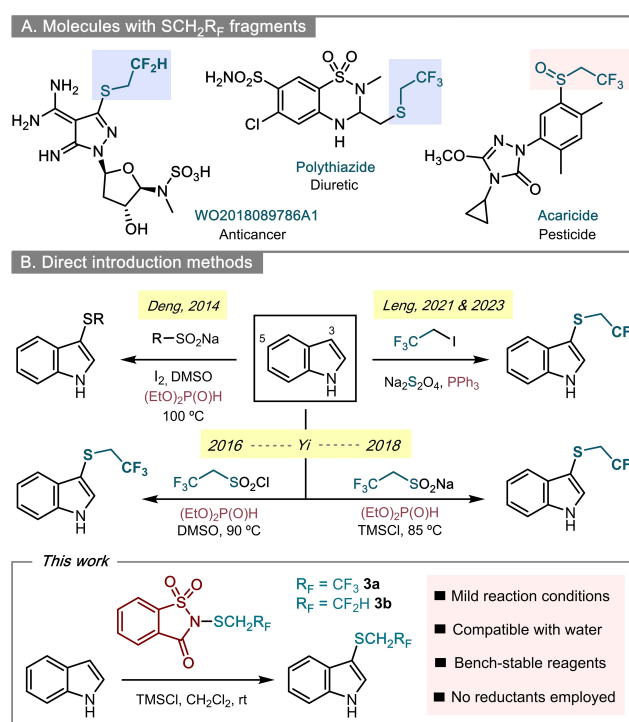
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Abstract: Two saccharine-based electrophilic reagents were developed for the direct introduction of SCH₂CF₃ and SCH₂CF₂H motifs *via* a C–S bond forming reaction. Their large-scale preparation and reactivity performance has been carefully examined, enabling access to a series of indoles through open-flask reactions. Sulfone and sulfoxide analogs (S(O)_nCH₂R_F, n = 1,2) are also accessible by sequential oxidation reactions.

Keywords: Chalcogens; Electrophilic reagents; Fluorine; Fluoroalkylthiolation; Indoles

Fluorinated substituents are widely employed in the design and development of pharmaceuticals, being present in 20% of FDA-approved drugs because of the particular properties conferred by such motifs.^[1] Among them, polyfluoroalkylthioether groups have attracted special interest due to their high lipophilic character, evidenced by the Hansch parameter (*e.g.*, CF₃, 0.88 vs. SCF₃, 1.44),^[2] that improves metabolic stability and membrane permeability, increasing the overall bioavailability of the compound.^[3] In this context, di- and trifluoroethylthio motifs (SCH₂CF₂H and SCH₂CF₃) are key functionalities in some pharmaceuticals and agrochemicals (Scheme 1A).^[4] Moreover, their oxidized analogs, sulfone and sulfoxide (S(O)_nCH₂R_F, n = 1,2), are also present in molecules with bioactive properties such as painkillers,^[5] selective estrogen receptor modulators (SERMs),^[6] acaricides, or insecticides.^[7]



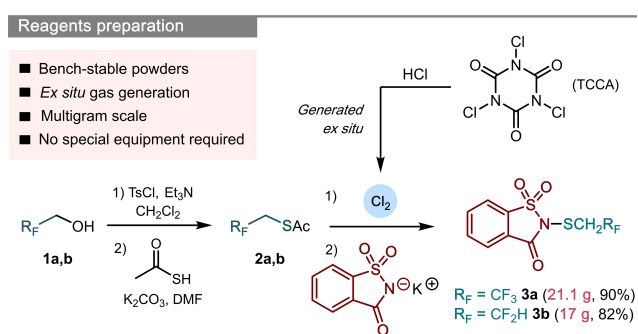
Scheme 1. (A) Selected molecules with biological activity containing some S(O)_nCH₂R_F (n = 0,1) fragments. (B) Reported methodologies for the direct introduction of SCH₂R_F groups into indoles, and this work. TMS = trimethylsilyl, DMSO = dimethylsulfoxide.

Commonly, these groups are constructed indirectly by polyfluoroalkylation of thiols (*via* S–R_F disconnections).^[8–10] However, a preinstalled sulfur

handle is required in this case, thus limiting the scope and leading to *de novo* synthesis as the only approach to access such molecular structures. Therefore, the synthesis of reagents capable of performing direct polyfluoroethylthiolations (*via* C–SR_F disconnections) by C–H functionalization is desirable and particularly useful when integrated with diversity-oriented strategies (DOS).^[11] In the context of biorelevant scaffolds, indole derivatives are ubiquitous heterocycles in naturally-occurring molecules and occupy a prominent place in drug development.^[12] Although the aromatic bicyclic structure offers multiple sites for substitution, databases reveal that the most prevalent positions for substitution are C3 (83%) and/or C5 (71%).^[13] Thus, several groups have worked on the modification of indoles with polyfluoroalkylthioether motifs.

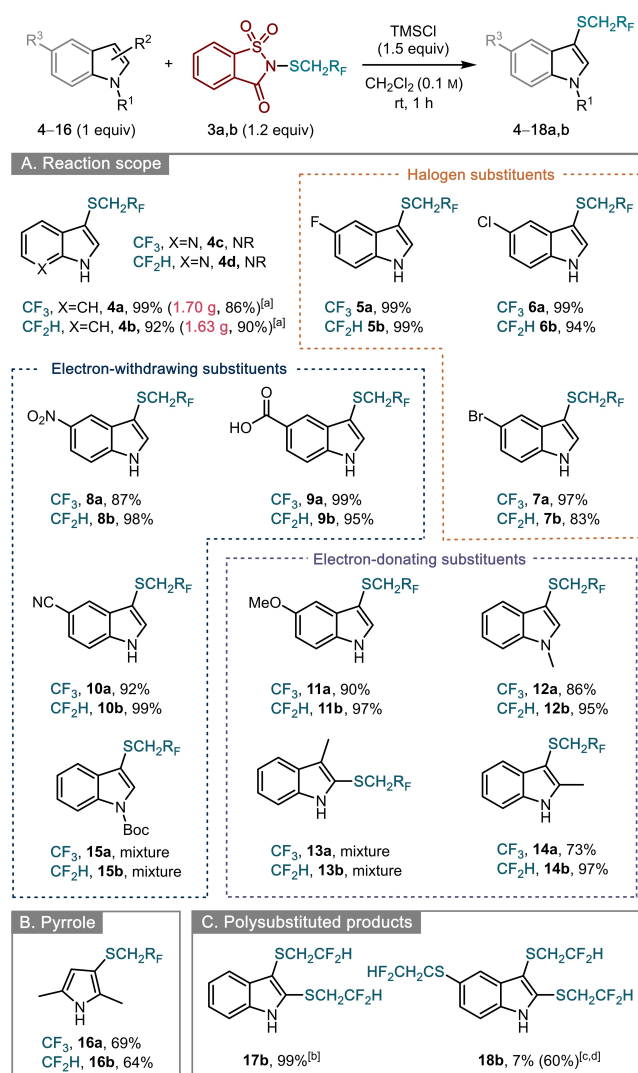
In 2014, Deng and co-workers presented sulfinates as reagents for incorporating SR_F fragments into indoles, using iodine as a catalyst (Scheme 1B).^[14] In 2018, Yi expanded this sulfinate-based methodology to introduce SCH₂CF₃ chains,^[15] using diethyl phosphite as a reductant. This reagent also promoted an analogous transformation using sulfonyl chlorides as precursors for the incorporation of SCH₂R_F chains.^[16] More recently, Leng developed a similar strategy for the trifluoroethylthiolation of indoles using a CH₂F_yCH₂I/Na₂S₂O₄/PPh₃ system,^[17] which was subsequently upgraded to avoid the use of phosphines.^[18] Although these methods facilitate the incorporation of thiofluoroalkyl groups, they use harsh reaction conditions, iodinated chains, and additives such as metal catalysts or reducing agents that are usually volatile and expensive. Recently, our group reported two bench-stable electrophilic reagents for the direct introduction of SCF₂CF₂H and SCF₂CF₃ motifs that are readily synthesized from cheap precursors and display a good reactivity/stability balance.^[19] These reagents belong to the family of *N*-SR_F scaffolds that have been widely used for the electrophilic and radical introduction of SCF₃ and SCF₂H motifs.^[20]

Herein, we develop two more electrophilic *N*-SCH₂R_F-type reagents **3 a, b** for the direct introduction of thiofluoroalkyl groups SCH₂CF₃ and SCH₂CF₂H to further complement the polyfluoroethylthiolation reagents toolbox with motifs bearing a spacer between the sulfur and the fluoroalkyl chain (R_F). A robust, 4-step synthesis was proposed for their preparation (Scheme 2). First, thioacetyl intermediates **2 a, b** were easily obtained in good yields (up to 98%) after tosylation and subsequent thioacetylation of commercially available alcohols **1 a, b**. Next, chlorination of **2 a, b** delivered the corresponding sulfonyl chlorides, which were subsequently reacted with potassium saccharin salt to afford the desired reagents **3 a, b** in gram scale (up to 21.1 g of **3 a** and up to 17 g of **3 b**) and excellent yields (up to 90%).



Scheme 2. Synthesis of **3 a, b** from commercially available alcohols **1 a, b**. See the SI for details. TCCA = trichloroisocyanuric acid, DMF = *N,N*-dimethylformamide.

Reagents **3 a, b** proved to be bench-stable powders with no decomposition observed when stored up to two years at -20°C . Moreover, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and stability studies at different working/storage temperatures demonstrated the robust stability of both reagents in the *solid state* and *in solution* (Supporting information (SI), Figures S1–S3). With these reagents in hand, a series of indoles were selected to evaluate the installation of SCH₂R_F fragments (Scheme 3A). Initial attempts on the direct reaction of **3 a** with 1*H*-indole **4** resulted in slow conversion rates. However, the addition of 1.5 equiv. of trimethylsilyl chloride (TMSCl),^[21] which generates the corresponding electrophilic R_FCH₂SCl species *in situ* (SI, Figures S6–S7), significantly enhanced the formation of **4 a** in quantitative yield. Similarly, reaction with **3 b** rendered the difluoroethylated product **4 b** in excellent yield (92%). Large-scale reactions (8.5 mmol), afforded gram amounts of the corresponding products **4 a** and **4 b** in 86% and 90% yield, respectively. Noteworthy, further purification was not required as the reaction mixtures were substantially clean, containing only an excess of saccharine that could be readily removed through repeated washings with saturated aqueous NaHCO₃. With the optimized reaction conditions in hand, we next evaluated a series of halo-substituted indoles **5–7** that afforded products **5–7 a, b** in good to excellent yields (up to 99%). The use of more electron-withdrawing substituents as nitro-, carboxylic acid, and cyano-, had no noticeable effect on the yields obtained in **8–10 a, b** (up to 99%). Reaction with electron-donating substituents such as 5-methoxy- delivered products **11 a** and **11 b** in 90% and 97% yield, respectively. When using a 2-methyl-substituted indole, **14 a** was obtained in 73% yield while **14 b** in 97%. We found that methyl substitution at the *N*-position of indole had almost no influence in the yields obtained (86% for **12 a** and 95% for **12 b**). Unfortunately, the presence of a deactivating substituent either at the nitrogen (*N*-Boc **15 a, b**) or within the benzene



Scheme 3. (A) Scope of indoles, (B) pyrrole, and (C) polysubstituted products. *General conditions:* indole/pyrrole (0.3 mmol), **3a,b** (0.36 mmol), and TMSCl (0.45 mmol) in CH₂Cl₂ (0.1 M). Isolated yields given unless otherwise indicated.^[a] 1*H*-indole (8.5 mmol), **3a,b** (10.2 mmol), and TMSCl (12.8 mmol) in CH₂Cl₂ (0.1 M).^[b] 1*H*-indole (0.3 mmol), **3a,b** (0.6 mmol), and TMSCl (0.9 mmol) in CH₂Cl₂ (0.1 M).^[c] 1*H*-indole (0.3 mmol), **3b** (1.2 mmol), and TMSCl (1.8 mmol) in CH₂Cl₂ (0.1 M).^[d] The low isolated yield in **18b** was due to decomposition upon purification. The yield in parenthesis was determined by ¹⁹F NMR. See the SI for details. NR = no reaction. Boc = tert-butoxycarbonyl.

ring (7-azaindole **4c,d**), eroded or suppressed the reactivity. The same occurs in **13a,b** as the most reactive C3 position of the heterocycle^[22] is occupied by a methyl substituent. Finally, we tested other systems such as 2,5-dimethylpyrrole **16** to obtain the corresponding SCH₂R_F-substituted products **16a** and **16b** in 69% and 64% yield, respectively (Scheme 3B). Bearing in mind the pronounced nucleophilicity of indoles,^[23] we investigated whether it was possible to

obtain polysubstituted products. Thus, by adding 2 equiv. of **3b**, disubstituted product **17b** was obtained in quantitative yield (Scheme 3C). Furthermore, by increasing the excess of the same reagent up to 4 equiv., the reaction can be further pushed to achieve trisubstituted product **18b** (60% by ¹⁹F NMR), albeit with a low isolated yield (7%) due to the decomposition observed after chromatographic purification.

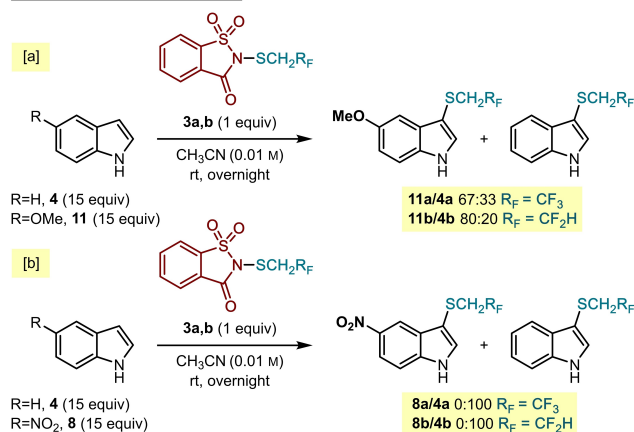
We next explored the impact of the electronic profile of the indoles on the reactions rate. Since the reaction involves an aromatic electrophilic substitution, it was hypothesized that those substrates with electron-donating substituents would be more reactive and show faster reaction kinetics than those containing electron-withdrawing groups.

Thus, competition experiments were carried out under pseudo-first order conditions, using an excess of indole pairs **4**, **11** (and **4**, **8**) that were reacted with reagents **3a,b** and their conversion measured. In the first case, there was a clear tendency towards the formation of products **11a,b** over **4a,b** (**11a/4a** 67:33 and **11b/4b** 80:20) while in the second case, there was a preference for the formation of **4a,b** instead of **8a,b** (**8a/4a** and **8b/4b** 0:100) (Scheme 4A) (SI, Figures S4–S5). Given the observed differences in reactivity, it was concluded that the reagents are capable of discriminating towards certain substrates, enabling selective transformations of electron-rich heterocycles over deactivated systems.

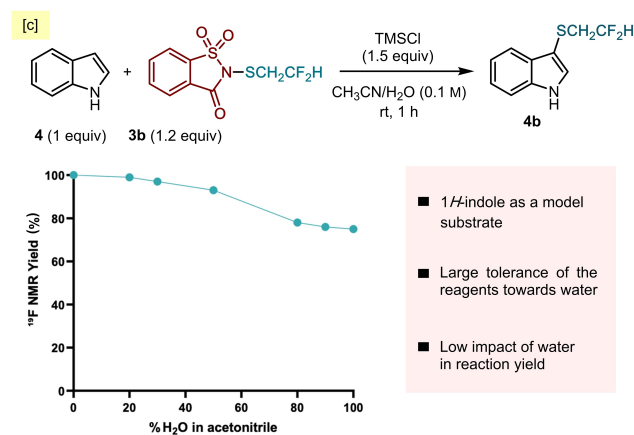
Having demonstrated the performance of reagents **3a** and **3b** with diversely substituted indoles, we sought to evaluate their water compatibility, which is an important point for the prospective use of these reagents in a greener and sustainable context.^[24] To do so, we conducted a series of experiments using 1*H*-indole **4** and reagent **3b** in mixtures of water and acetonitrile (Scheme 4B). To our surprise, water had a relatively low impact in the reaction. By using a 50% mixture of water and acetonitrile, the reaction yield only dropped 7% from the initial conditions (dry acetonitrile and quantitative yield). When using pure water as solvent, the reaction was not deterred and we were able to obtain product **4b** in 75% yield. This observation suggests that the reaction is fast enough to compensate the effect of the degradation rate of the reagent when water is introduced (SI, Figure S1). Notably, this tolerance enables the performance of the reactions without the need to exclude water from the flask or take additional measures (open-flask reactions).

Taking advantage of polyfluoroethylthio moieties as derivatization handles, a variety of transformations were performed. Thus, indole derivatives **4a** and **4b** were oxidized to the corresponding sulfones using hydrogen peroxide and ammonium molybdate tetrahydrate, affording **19a** and **19b** in 77% and 99% yield, respectively. In contrast, sulfoxide products were

A. Competition experiments



B. Water tolerance

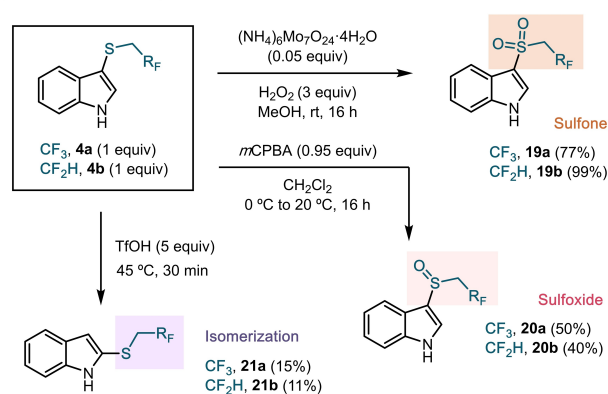


Scheme 4. (A) Competition and (B) water tolerance experiments.^[a] 1*H*-indole **4** (0.75 mmol), 5-methoxy-1*H*-indole **11** (0.75 mmol), and **3a** (0.05 mmol) in CH₃CN (0.01 M).^[b] 1*H*-indole **4** (0.75 mmol), 5-nitro-1*H*-indole **8** (0.75 mmol), and **3a** (0.05 mmol) in CH₃CN (0.01 M).^[c] 1*H*-indole **4** (0.1 mmol), **3b** (0.11 mmol), and TMSCl (0.15 mmol) in CH₃CN/H₂O (0.1 M). See the SI for details.

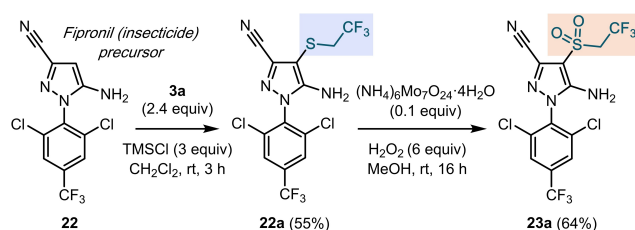
selectively obtained when *m*CPBA was employed, delivering **20a** (50%) and **20b** (40%) in moderate yields. Next, C3-to-C2-isomerization reactions were carried out to access 2-(polyfluoroalkylthio)-indoles, which enabled access to a range of substituted indoles difficult to obtain by conventional reactions (see **13a, b** in Scheme 3). Based on literature procedures,^[25] treatment of **4a** and **4b** with TfOH afforded **21a** and **21b** in only 30 min at 45 °C, albeit in low yields (Scheme 5A). Finally, the application of reagent **3a** was also tested on the agrochemical intermediate **22** (pyrazole scaffold) to afford Fipronil derivative (insecticide) **22a** in 55% yield, which was subsequently oxidized to the potential sulfone metabolite **23a** (42%) (Scheme 5B).

In summary, two bench-stable electrophilic reagents have been disclosed for the direct introduction of

A. Derivatizations



B. Agrochemical modification



Scheme 5. (A) Derivatization reactions and (B) Agrochemical modification. See the SI for details. *m*CPBA = meta-chloroperbenzoic acid.

SCH₂CF₃ and SCH₂CF₂H motifs following a 4-step synthetic route. These readily available reagents are suitable for the di- and trifluoroethylthiolation of a variety of indoles and other electron-rich heterocycles such as pyrrole and pyrazole. The reaction proved to be robust to scale up and compatible with water as a solvent. Competition experiments demonstrated the sensitivity of the reagents to the electronic properties of the substrates, enabling selective transformations. Finally, product derivatization to sulfoxides, sulfones, and C2-substituted compounds demonstrated the potential of our reagents to streamline the preparation of SR_F scaffolds as pivotal motifs for the medicinal chemistry community.

Experimental Section

General Procedure A1 for Tosylation (S1 a, b)

To a 2 L round-bottom flask, equipped with a magnetic stir bar, Et₃N (2 equiv.) was added to a solution of the corresponding commercially available alcohol **1a, b** (1 equiv.) in CH₂Cl₂ (1 M) at room temperature. The mixture was cooled at 0 °C using an ice/water bath and tosyl chloride (1 equiv.) was added portion-wise over a period of 30 min. The mixture was stirred at 0 °C for 30 min and then at room temperature for 16 h. The reaction mixture was cooled to 0 °C and acidified using 10% aqueous HCl (500 mL) under vigorous stirring. After 15 min, the mixture was transferred to an extraction funnel, additional water (500 mL) was added, and the organic layer was separated. The

aqueous phase was extracted with CH_2Cl_2 (3×200 mL) and the combined organic fractions were dried with Na_2SO_4 , filtered, and the solvent evaporated under reduced pressure. The crude products **S1a,b** were used in the next step without further purification.

General Procedure A2 for Thioacetylation (**2a, b**)

To a flask containing K_2CO_3 (1.5 equiv.) and dimethylsulfoxide (DMSO, 2 M), thioacetic acid (3 equiv.) was added under argon at 0°C during a period of 20 min and stirred at room temperature for 1 h. After addition of tosylates **S1a,b** (1 equiv.) at room temperature, the mixture was stirred at 40°C for 24 h. The mixture was then diluted with CH_2Cl_2 (400 mL) and water (1 L) transferred to an extraction funnel, the organic layer was separated, and the aqueous phase further extracted with CH_2Cl_2 (3×100 mL). The combined organic fractions were dried with Na_2SO_4 , filtered, and the product distilled under reduced pressure to obtain the corresponding thioacetates **2a,b**, which were used in the next step without further purification.

General Procedure A3 for Sulfenyl Chlorides (**S2a, b**)

A round-bottom flask, equipped with a magnetic stir bar, was charged with **2a,b** (1 equiv.). The flask was then evacuated and backfilled with argon three times. Subsequently, anhydrous CHCl_3 (20 mL) for **2a** (and anhydrous 1,2-DCE (60 mL) for **2b**) were added using a syringe. Then, a chlorine stream was passed through the solution for 15 min. The crude reaction was distilled under reduced pressure and moderate heating (20 mbar, 35°C) to afford a solution of fluoroethanesulfonyl chloride in CHCl_3 for **S2a** (in 1,2-DCE for **S2b**). An aliquot was transferred to an NMR tube and quantitative ^{19}F NMR analysis indicated a concentration of 0.17 M of **S2a** in CHCl_3 (and 0.97 M of **S2b** in 1,2-DCE). These solutions were used in the next step without further purification.

General Procedure A4 for Electrophilic Reagents (**3a, b**)

A round-bottom flask, equipped with a magnetic stir bar, was charged with potassium saccharin salt (0.95 equiv.). The flask was then evacuated and backfilled with argon three times. Subsequently, the flask was cooled down to 0°C and a solution of fluoroethanesulfonyl chloride **S2a,b** (1.0 equiv.) was added. The mixture was stirred at room temperature for 1 h, filtered through Celite®, and concentrated under reduced pressure to afford the desired electrophilic reagents **3a,b**.

General Procedure B for Di- and Trifluoroethylation of Indoles and Pyrrole (**4–18a, b**)

A 25 mL round-bottom flask, equipped with a magnetic stir bar, was charged with indole (1 equiv.) and CH_2Cl_2 (or CDCl_3) (0.1 M). Then, the mixture was cooled down to 0°C and **3a,b** (1.2 equiv. for **3a** and 1.0 equiv. for **3b**) and TMSCl (1.5 equiv.) were added sequentially. The mixture was stirred at room temperature for 3 h, monitoring the progress of the

reaction by TLC. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography.

General Procedure C1 for Sulfones (**19a, b**)

A 25 mL round-bottom flask, equipped with a magnetic stir bar, was charged with indole (1.0 equiv.), ammonium molybdate tetrahydrate (0.05 equiv.) and MeOH (0.2 M). Then, H_2O_2 (30% (w/w) in H_2O) (3.0 equiv.) was added and the mixture was stirred at room temperature overnight, monitoring the progress of the reaction by TLC. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography.

General Procedure C2 for Sulfoxides (**20a, b**)

A 5 mL round-bottom flask, equipped with a magnetic stir bar, was charged with indole (1.0 equiv.) and CH_2Cl_2 (0.33 M). Then, the mixture was cooled down to 0°C and *m*CPBA (0.95 equiv.) was added. The mixture was stirred at room temperature overnight, monitoring the progress of the reaction by TLC. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography.

General Procedure C3 for Isomerization Reactions (**21a, b**)

A 5 mL round-bottom flask, equipped with a magnetic stir bar, was charged with indole (1.0 equiv.). Then, TFOH (5.0 equiv.) was added and the mixture was stirred at 45°C for 30 min, monitoring the progress of the reaction by TLC. Upon completion, the reaction mixture was diluted with ethyl acetate, washed with water, extracted with sodium carbonate followed by brine, and purified by flash column chromatography.

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References


- [1] a) J. Wang, M. Sánchez-Roselló, J. Aceña, C. Del Pozo, A. Sorochinsky, S. Fustero, V. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; b) B. M. Johnson, Y. Z. Shu, X. Zhuo, N. A. Meanwell, *J. Med. Chem.* **2020**, *63*, 6315–6386; c) P. Bhutani, G. Joshi, N. Raja, N. Bachhav, P. Rajann, H. Bhutani, A. Paul, R. Kumar, *J. Med. Chem.* **2021**, *64*, 2339–2381; d) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640;

- e) I. Ojima, in *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**.
- [2] a) T. Fujita, J. Iwasa, C. Hansch, *J. Am. Chem. Soc.* **1964**, *86*, 5175–5180; b) I. Rico, C. Wakselhan, *Tetrahedron Lett.* **1981**, *22*, 323–326.
- [3] a) C. Ni, M. Hu, J. Hu, *Chem. Rev.* **2015**, *115*, 765–825; b) E. Ilardi, E. Vitaku, J. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832–2842; c) T. Milcent, B. Crousse, in *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*, J.-A. Ma, D. Cahard, **2020**.
- [4] a) K. A. Adrien, B. Alig, A. Becker, A. Voerste, U. Goergens, WO2013092350A1, **2013**; b) S. Adhikari, E. Frances, D. Bradley, A. E. Gould, S. J. Harrison, S. Huang, L. Ma, WO2018089786A1, **2019**.
- [5] S. Schunk, M. Reich, R. M. Koenigs, US2017101397 A1, **2017**.
- [6] R. D. Dally, J. A. Dodge, S. A. Frank, S. A. Jones, T. A. Shepherd, O. B. Wallace, K. C. Fong, C. W. Hummel, G. S. Lewis, WO2004009086A1, **2004**.
- [7] a) M. Steinman, J. G. Topliss, R. Alekel, Y. S. Wong, E. E. York, *J. Med. Chem.* **1973**, *16*, 1354–1360; b) B. Alig, S. Cerezo-Galvez, R. Fischer, A. Koehler, J. J. Hahn, A. Becker, K. Ilg, A. Voerste, D. Portz, WO2014202510A1, **2014**; c) B. Alig, S. Antons, R. Fischer, N. Lui, A. Koehler, A. Voerste, U. Goergens, US2011046194A1, **2011**.
- [8] S. Cheng, M. Zhang, X. Liao, Z. Weng, *J. Org. Chem.* **2016**, *81*, 7993–8000.
- [9] S. Huang, Z. Xia, K. Lu, H. Lu, C. Tung, Z. Xu, *Chin. J. Chem.* **2020**, *38*, 1625–1628.
- [10] P. J. Foth, F. Gu, T. G. Bolduc, S. S. Kanani, G. M. Sammis, *Chem. Sci.* **2019**, *10*, 10331–10335.
- [11] a) X. Pannecoucke, T. Besset, *Org. Biomol. Chem.* **2019**, *17*, 1683–1693; b) J. Zhang, J. Yang, H. Zheng, X. Xue, H. Mayr, J. Cheng, *Angew. Chem. Int. Ed.* **2018**, *57*, 12690–12695; c) H. Chachignon, D. Cahard, *Chin. J. Chem.* **2016**, *34*, 445–454; d) F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415–2428.
- [12] a) T. V. Sravanthi, S. L. Manju, *Eur. J. Pharm. Sci.* **2016**, *91*, 1–10; b) N. Chadha, O. Silakari, *Eur. J. Med. Chem.* **2017**, *134*, 159–184; c) Z. Deng, L. Qiu, J. Cheng, H. Zhang, W. Cao, X. Tang, *Adv. Synth. Catal.* **2023**, *365*, 693–698.
- [13] E. Vitaju, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
- [14] F. Xiao, H. Xie, S. Liu, G. Deng, *Adv. Synth. Catal.* **2014**, *356*, 364–368.
- [15] R. Wang, L. Jiang, W. Yi, *J. Org. Chem.* **2018**, *83*, 7789–7798.
- [16] L. Jiang, W. Yi, Q. Liu, *Adv. Synth. Catal.* **2016**, *358*, 3700–3705.
- [17] F. Leng, J. Huang, N. Yu, G. Wang, *Tetrahedron Lett.* **2021**, *85*, 153488.
- [18] N. Yu, J. Huang, F. Leng, *RSC Adv.* **2023**, *13*, 730–733.
- [19] J. Mestre, M. Bernús, S. Castellón, O. Boutureira, *J. Org. Chem.* **2022**, *87*, 10791–10806.
- [20] a) X. Shao, C. Xu, L. Lu, Q. Shen, *Acc. Chem. Res.* **2015**, *48*, 1227–1236; b) Q. Shen, *J. Org. Chem.* **2023**, *88*, 3359–3371; c) D. Zhu, X. Hong, D. Li, L. Lu, Q. Shen, *Org. Process Res. Dev.* **2017**, *21*, 1383–1387; d) C. Hu, F. Chen, G. Lu, W. Yi, *Chin. Chem. Lett.* **2022**, *33*, 4293–4297; e) D. Zhu, Y. Gu, L. Lu, Q. Shen, *J. Am. Chem. Soc.* **2015**, *137*, 10547–10553; f) S. Mukherjee, T. Patra, F. Glorius, *ACS Catal.* **2018**, *8*, 5842–5946; g) C. Ghiazza, T. Billard, A. Tlili, *Chem. Eur. J.* **2019**, *25*, 6482–6495; h) R. Honeker, R. A. Garza-Sanchez, M. N. Hopkinson, F. Glorius, *Chem. Eur. J.* **2016**, *22*, 4395–4399; i) G. Dagousset, C. Simon, E. Anselmi, B. Tuccio, T. Billard, E. Magnier, *Chem. Eur. J.* **2017**, *23*, 4282–4286.
- [21] a) C. Xu, B. Ma, Q. Shen, *Angew. Chem.* **2014**, *126*, 9470–9474; b) P. Zhang, M. Li, X. S. Xue, C. Xu, Q. Zhao, Y. Liu, H. Whang, Y. Guo, L. Luo, Q. Shen, *J. Org. Chem.* **2016**, *81*, 7486–7509.
- [22] a) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; b) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449–4465.
- [23] R. J. Sundberg, in *the Chemistry of Indoles*, Academic Press, New York, **1970**.
- [24] Q. Pang, W. Zuo, Y. Zhang, X. Li, B. Han, *Chem. Rec.* **2023**, *23*, e20220289.
- [25] P. Csomós, L. Fodor, G. Bernáth, A. Csámpai, P. Sohár, *Tetrahedron* **2009**, *65*, 1475–1480.

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