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# An Efficient Synthesis of Substituted Pyrazoles from One-Pot Reaction of Ketones, Aldehydes, and Hydrazine Monohydrochloride

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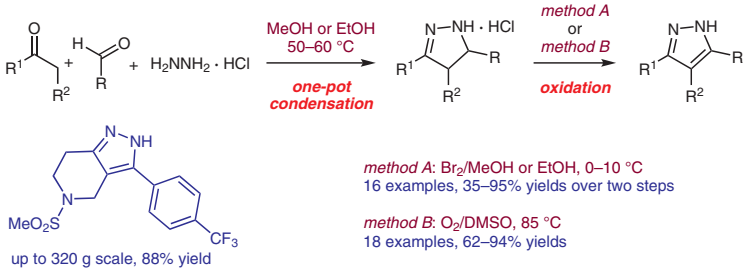


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**Abstract** An efficient, one-pot and metal-free process for the preparation of 3,5-disubstituted and 3,4,5-trisubstituted pyrazoles on multigram scale was developed. One-pot condensation of ketones, aldehydes and hydrazine monohydrochloride readily formed pyrazoline intermediates under mild conditions. Oxidation of pyrazolines, *in situ*, employing bromine afforded a wide variety of pyrazoles. The methodology offers a fast, and often chromatography-free protocol for the synthesis of 3,4,5-substituted pyrazoles in good to excellent yields. Alternatively, a more benign oxidation protocol affords 3,5-disubstituted or 3,4,5-trisubstituted pyrazoles by simply heating pyrazolines in DMSO under oxygen.

**Key words** heterocyclic compounds, pyrazoles, pyrazolines, ketones, aldehydes, oxidation of pyrazolines, oxygen, bromine

Pyrazoles represent an important family of heterocycles, covering a broad range of synthetic as well as natural products that display diverse chemical, biological, agrochemical, and pharmacological properties.[1] They are particularly ubiquitous pharmacologically active agents even though their occurrence in nature is less abundant (Figure 1). A number of important drugs containing a pyrazole pharmacophore such as *Celecoxib*, *Sildenafil*, *Rimonabant*, and *Lersivirine* have been developed.[2–5] These drugs display different mechanisms of action. For example, *Celecoxib*[2] demonstrates anti-inflammatory effects and inhibits COX-2; *Rimonabant*[3] functions as a cannabinoid receptor and is used to treat obesity. *Sildenafil*[4] is known to inhibit phosphodiesterase and *Lersivirine*[5] is an anti-HIV candidate. The importance of this class of heterocycles as medicinal agents has inspired the pursuit of general and efficient syntheses.[6] Among many existing approaches to pyrazoles, Knorr synthesis[7] employing 1,3-diketones and hydrazines serves as a reliable entry. Alternatively, condensation of α,β-unsaturated ketones with hydrazine and subsequent oxidation of pyrazoline leads to pyrazole (Scheme 1).[8] Herein, we report a simple synthesis of pyrazolines from one-pot condensation of ketones, aldehydes, and hydrazine monohydrochloride and efficient oxidation of pyrozolines using either bromine or an environmentally benign oxidizer, oxygen.

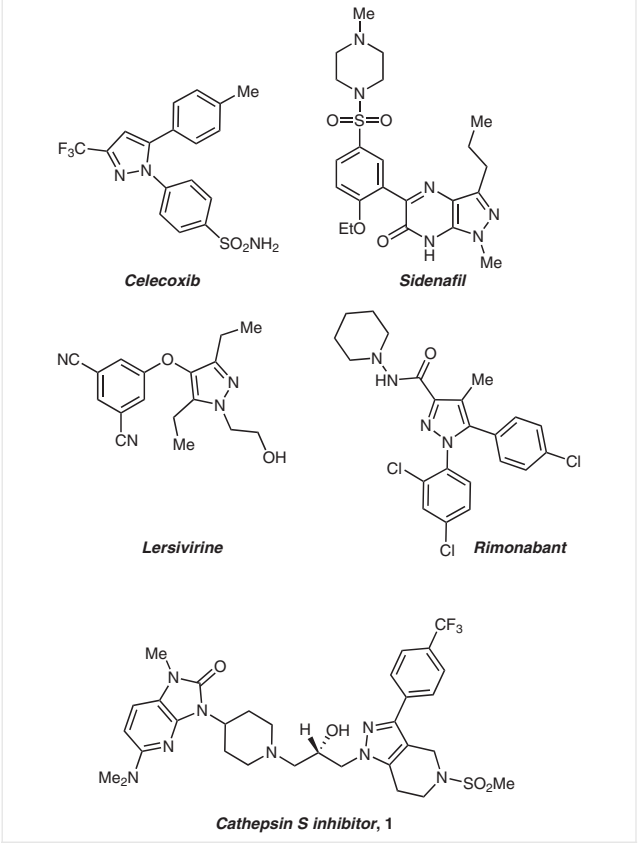


**Figure 1** Pyrazoles as biological active agents

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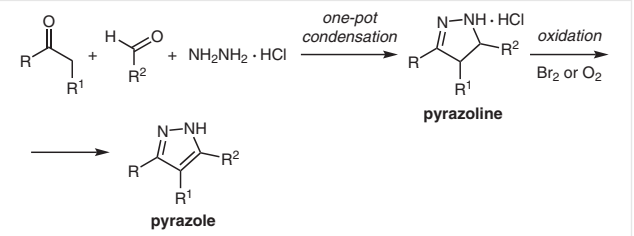
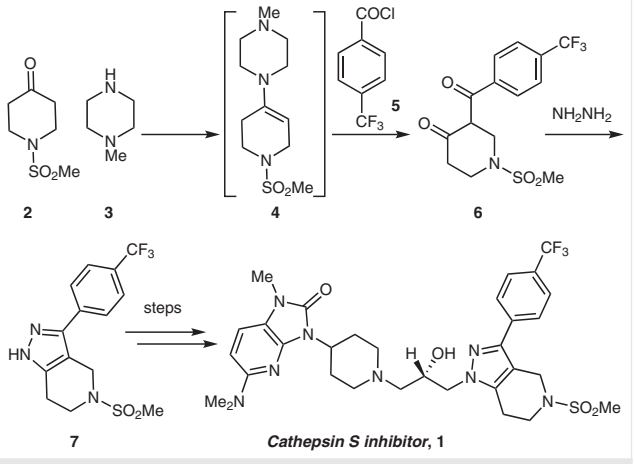



**Scheme 1** One-pot, three-component coupling, and subsequent oxidation for the synthesis of pyrazole

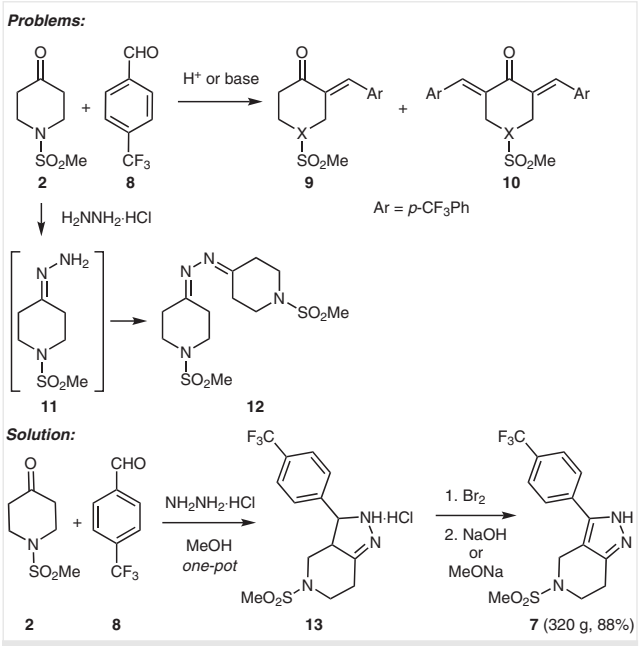
Compound **1** (Figure 1) bearing a pyrazole moiety is a potent cathepsin S inhibitor that was developed for the treatment of autoimmune disease such as lupus, rheumatoid arthritis, and asthma.[9] It was prepared from the key intermediate pyrrole **7** which, in turn, was prepared from diketone **6** using a Knorr condensation reaction. Formation of enamine **4**, *in situ*, followed by acylation afforded 1,3-diketone **6** in 50% yield on multigram scale over two steps. Unfortunately, the reaction failed to scale-up and resulted in a significantly lower yield (20%) due to incomplete formation of enamine **4** (Scheme 2). Attempts to improve this reaction were fruitless, including using enone at the acylation step.[10] We then turned our attention to an alternative method employing condensation of the α,β-unsaturated ketones with hydrazine or its HCl salt to form pyrazoline and subsequent oxidation.




**Scheme 2** Synthesis of *Cathepsin S* inhibitor, **1**

As shown in Scheme 3, we met unexpected challenges when attempting to prepare enone **9** from ketone **2** usingl the conventional Claisen–Schmidt method.[11] The reaction was plagued by the double condensation to form enone **10** as the major side product. Removal of this byproduct *via* crystallization was not feasible since both compounds (**9** and **10**) cocrystallized. Column chromatography had to be employed to purify **9**, which was not viable for large scale. Running the reaction under acidic conditions led exclusively to formation of bis(alkylidene) derivative **10**.

We next tested a three-component reaction of cyclohexanone **2**, hydrazine hydrochloride, and aldehyde **8** in methanol. We were delighted to find that the reaction completed in <0.5 h at 50–60 °C to afford pyrazoline **13** quantitatively. The desired pyrazoline **13** was directly isolated as the HCl salt from the reaction mixture. We noted that the rate of reaction was independent of the addition order of reagents. Preformation of hydrazone **11** from ketone **2** and hydrazine in the absence of aldehyde only afforded poorly soluble azine **12**.[12] Furthermore, the choice of solvent had a strong impact on the efficiency of the reaction. For example, reactions run in a nonpolar solvent such as toluene only afforded a complex mixture with <10 % of **13**. Running reaction in either NMP or water only gave **13** in moderate 58% and 69% yield. Methanol gave a much higher. The pyrazoline HCl salt was readily oxidized by liquid bromine to afford pyrazole **7** in 88% isolated yield over this very simple three-step sequence on 320 g scale. Intermediate **7** was next employed in the large-scale synthesis of compound **1**. We noted that using hydrazine monohydrochloride was essential for the success of the reaction.




**Scheme 3** Development of one-pot process to pyrazole **7**

The one-pot procedure for the preparation of pyrazole **7** was next extended to other ketones and aldehydes. We were delighted to find that the protocol could be readily applied to cyclohexanone with many aldehydes to afford pyrazoles (**14a–h**) in 65–95% yield. (Scheme 4). Introduction of pyridinyl groups to the pyrazole was feasible with both 2- and 4-pyridinecarboxaldehydes to afford pyrazoles **14i** and **14j** in 53% and 60% yield. Employing 3-methylcyclohexanone led to formation of pyrazole **14k** and **14l** in a high regioselectivity (11:1). A highlight for the reaction is the

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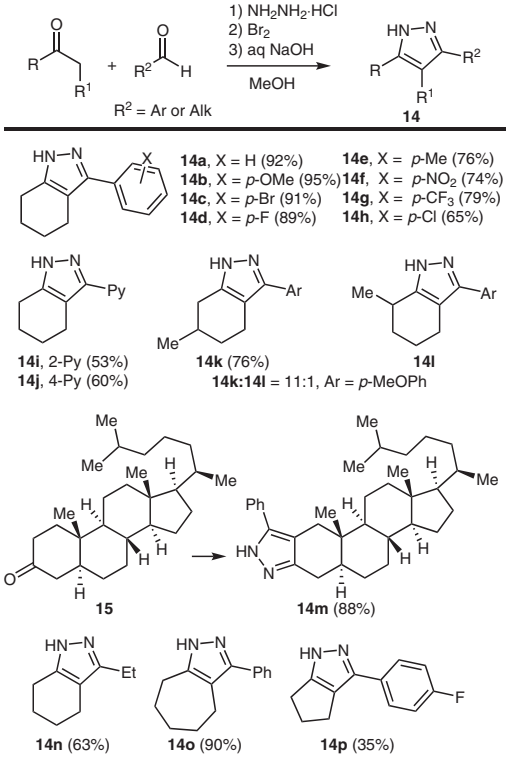
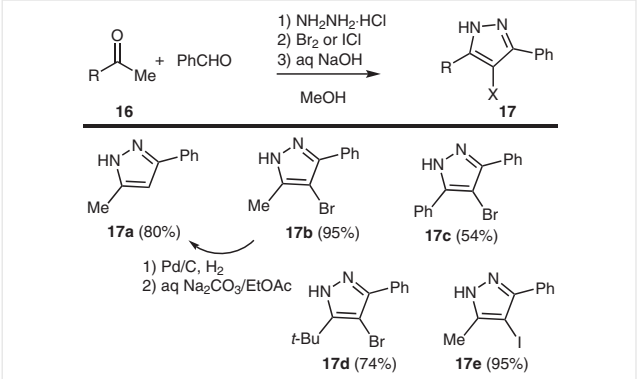
modification of steroid ketone **15** with pyrazole moiety to afford **14m** in 88% yield.[13] Using aliphatic aldehydes such as *n*-propyl aldehyde afforded the desired pyrazole **14n** in 63% yield. The reaction was further extended to cycloheptanone, with pyrazole **14o** prepared in 90% yield. The efficiency decreased when cyclopentanone was used, giving pyrazole **14p** in low yield.




**Scheme 4** One-pot synthesis of pyrazoles from cyclic ketones and aldehydes

The reaction using cyclic ketones was next applied to acyclic ketones. Overbromination of the pyrazole occurred to afford **17a** and **17b** as a mixture when acetone and benzaldehyde were tested using 1.3 equiv bromine. Pyrazole **17a** can be converted into **17b** with excess bromine. Thus, when 2 equiv bromine were used in the one-pot sequence, bromopyrazole **17b** was obtained in 95% yield. Similarly, phenyl and *tert*-butyl bromopyrazole **17c** and **17d** were prepared in 54% and 74% yield. Using ICl as oxidizer led to iodopyrazole **17e** in 95% yield. Catalytic hydrogenation of **17b** led to debromination effectively to give pyrazole **17a** in 80% yield (Scheme 5).

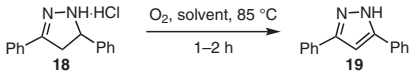
To directly prepare desbromopyrazoles like **17a**, we studied the oxidation step without bromine. We anticipated that this would lead to efficient synthesis of 3, 5-substituted pyrazoles without requiring debromination. We started the investigation using pyrazoline HCl salt **18** as the




**Scheme 5** Formation of halogenated pyrazoles

model substrate, believing that an oxidation using oxygen in the presence of a metal catalyst might be feasible to make 3,5-substituted pyrazole **19** (Table 1).[8b,14]

**Table 1** Dehydrogenation Screening of Pyrazoline **18**[a]




| Entry | Catalyst | Solvent | Yield (%) |
|---|---|---|---|
| 1 | 10 mol% $Cu(OAc)_2$ | DMSO | 91 |
| 2 | 1 mol% $Cu(OAc)_2$ | DMSO | 92 |
| 3 | none | DMSO | 91 |
| 4 | none | toluene | 64 |
| 5 | none | 1,4-dioxane | 64 |
| 6 | none | AcOH | 86 |

[a] Reaction concentration: 0.2 M.

At the onset of this new endeavor, we employed $Cu(OAc)_2$ (10 mol%) as catalyst and oxygen as terminal oxidant. The reaction proceeded smoothly, forming pyrazole in excellent yield under these milder conditions (Table 1, entry 1). A study on the catalyst loading revealed that even at 1 mol% the reaction proceeded smoothly. It was not until we conducted the control experiment that we realized the feasibility of oxidation without catalyst (Table 1, entry 3). A quick survey of solvents indicated that DMSO was superior to others, presumably due to higher solubility of oxygen. Reaction temperature also played a role. The conversion at lower temperature, such as 45 °C, was poor. Higher reaction temperatures, such as 125 °C, resulted in a messy reaction. The reaction is also dependent on the concentration of oxygen used. For example, faster and cleaner conversion was achieved with 100% oxygen than with 8% oxygen.

With the optimal reaction conditions in hand, we explored the scope and generality of the newly defined oxidation protocol to produce a wide variety of pyrazoles. As shown in Scheme 6, all the desired pyrazoles were readily

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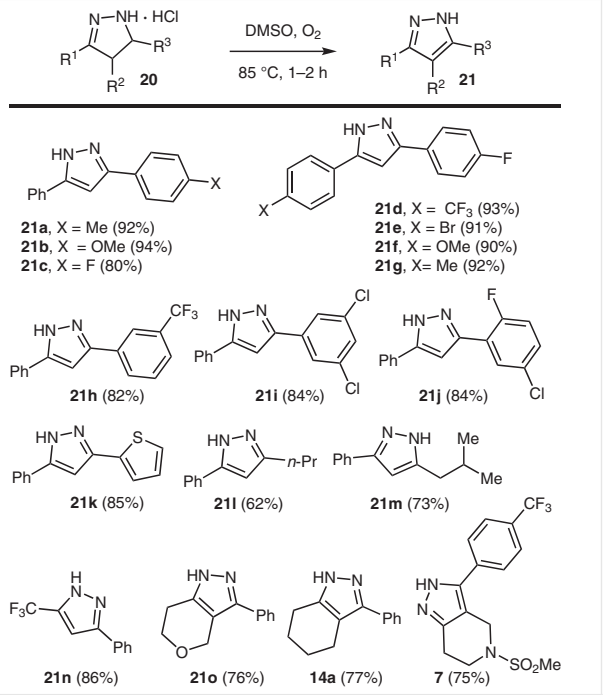
produced in excellent yields. The reaction tolerates a wide variety of substituents. Bisaryl-substituted pyrazoles **21a–j** were obtained in 80–94% yields. Heterocycles can be introduced, such as thiophene to make pyrazole **21k**. Good yields were also obtained for alkyl-substituted pyrazoles such as **21l–n**. Cyclohexyl- and tetrahydropyran-fused pyrazole derivatives **21o** and **14a** were readily prepared in 76% and 77% yield. Finally, pyrazole **7** was readily prepared in 75% yield (Scheme 6) without isolation of intermediate **13** (Scheme 3).




**Scheme 6** Dehydrogenation of pyrazolines using pure oxygen

In conclusion, we have developed an efficient, metal-free methodology for the preparation of 3,5-di- and 3,4,5-trisubstituted pyrazoles from readily available starting materials: ketone, aldehyde, and hydrazine HCl salt.[15] Simply mixing these reagents in methanol afforded pyrazolines, which were subsequent oxidized by either bromine or oxygen to give a wide variety of pyrazoles in good to excellent yields (53–98%). The synthetic protocol applying bromine is suitable for the preparation of 3,4,5-substituted pyrazoles whereas oxidation with oxygen leads to 3,5-disubstituted or 3,4,5-trisubstituted pyrazoles.[16] Using oxygen as terminal oxidant is a green alternative to bromine, as water is the only byproduct.

## Acknowledgment

We are grateful to the staff of the analytical laboratory in the Laboratory for Process Research, University of Zurich, for the LC MS, DSC and titration measurements, the staff of the NMR facility in the Department of Organic Chemistry, University of Zurich, for their help with the NMR studies on the 600 MHz spectrometer, and Ms. Huawei Ma and Ms. Huan Dong at Porton (Shanghai) R&D center for analytical support. We are also grateful Peter Jay Yao for thorough reviewing of our manuscript.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591941.

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(15) **General Procedure for One-Pot, Three-Component Coupling, and Subsequent Oxidation by Bromine for the Synthesis of Pyrazoles 14a–p and 7**

A suspension of hydrazine hydrochloride (6.85 g, 0.1 mol, 1 equiv) in MeOH (30 mL) was warmed under argon atmosphere to 55 °C. Ketone (0.1 mol, 1.0 equiv) and neat aldehyde (0.1 mol, 1.0 equiv) were added sequentially dropwise over 30 min to the stirred suspension. After 10 min of stirring the resulting orange solution was cooled to 0 °C over 1 h. Bromine (20.8 g, 0.13 mol, 1.3 equiv) was added dropwise to the reaction mixture with stirring, keeping the reaction temperature below 10 °C. After



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30 min of stirring at 0 °C, the reaction was quenched with dropwise addition of 30 wt% aqueous solution of NaOH (53.3 g, 0.4 mol, 4 equiv) over 1 h. The resulting heterogeneous mixture was warmed briefly to 45–55 °C and then cooled to 25 °C. The reaction mixture was stirred overnight to afford a suspension which was filtered. The collected solid was washed with water (60 mL) to afford crude product as wet solids. The wet solid in EtOH (35 mL) was heated at reflux for 30 min, cooled to 25 °C, stirred at this temperature for 1 h, and filtered. The collected solid was washed with EtOH (4–6 mL) and dried for 24 h at 65 °C under vacuum (2 mbar) to afford pyrazoles **14** or **7**.

**Analytical Data for Compound 14a**

$^1$H NMR (600 MHz, $CDCl_3$): δ = 8.42 (br s, 1 H, 1). 7.72 (dt, *J* = 7.0, 1.2 Hz, 2 H, 2′ phenyl), 7.44 (tt, *J* = 7.2, 1.1 Hz, 2 H, 3′ phenyl), 7.39 (tt, *J* = 7.4, 1.2 Hz, 1 H, 4′ phenyl), 2.72 (t, *J* = 6.1 Hz, 2 H, 4), 2.70 (t, *J* = 6.2 Hz, 2 H, 7), 1.87–1.80 (m, 4 H, 6 and 5). $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 145.0 (7a), 143.2 (3), 129.2 (4′ phenyl), 129.1 (1′ phenyl), 129.0 (3′ phenyl), 127.4 (2′ phenyl), 114.0 (3a), 22.9 (5), 21.9 (6), 21.7 (7), 21.5 (4). MS (LR-APCI$^+$): *m/z* calcd for $C_{13}H_{14}N_2$: 198.1; found: 199.0 [M + H]$^+$.

**Procedure for the Synthesis of 3,5-Substituted Pyrazole 17a by Catalytic Reduction of 4-Bromopyrazol 17b**

A suspension of hydrazine hydrochloride (6.85 g, 0.1 mol, 1 equiv) in MeOH (30 mL) is warmed under argon atmosphere to 55 °C. Acetone (5.80 g, 0.1 mol, 1 equiv) is mixed with the stirred suspension, then, within 30 min neat benzaldehyde (10.61 g, 0.1 mol, 1 equiv) is added dropwise to the reaction mixture. After 10 min of stirring the resulting orange solution is cooled to 0 °C. Bromine (31.96 g, 0.2 mol, 2 equiv) is added dropwise to the reaction mixture while stirring at temperature lower than 15 °C. After more than 30 min of the continuing stirring at 0–5 °C the reaction is quenched by slowly (over 1 h) adding of the 30% aqueous NaOH solution (53.33 g, 0.4 mol, 4 equiv). The resulting heterogeneous mixture is extracted with ethyl acetate (100 mL). From the separated organic layer solvent is removed. The residue, pyrazole **17b**, is submitted to a catalytic hydrogenation at 4 bar/80 °C with 5% wet Pd on activated charcoal (3 g, 1.4 mmol, 0.014 equiv) in EtOH (50 mL). After 10–20 h of hydrogenation, the reaction mixture is cooled, filtered over Celite, the cake is washed with EtOH (50 mL), and from combined mother liquors containing the product solvent is removed in vacuo. The isolated material is hydrobromide salt of pyrazole **7a** which is converted into free base by the basic extraction work-up in ethyl acetate/10% w/w aqueous solution of sodium carbonate.

**Analytical Data for Compound 17a**

$^1$H NMR (600 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.1 Hz, 2 H, 2′), 7.44 (t, *J* = 7.5 Hz, 2 H, 3′), 7.31 (tt, *J* = 7.4, 1.2 Hz, 1 H, 4′), 6.36 (s, 1 H, 4), 2.34 (d, *J* = 0.6 Hz, 3 H, $CH_3$-C5). $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 128.7 (1′ and 3′), 127.9 (4′), 125.6 (2′), 102.1 (4), 11.8 ($CH_3$), C3 and C5 missing. MS (LR-APCI$^+$): *m/z* calcd for $C_{10}H_{10}N_2$: 158.1; found: 158.9 [M + H]$^+$.

**Analytical Data for Compound 17b**

$^1$H NMR (600 MHz, $CDCl_3$): δ = 7.75 (dt, *J* = 7.0, 1.5 Hz, 2 H, 2′), 7.43 (tt, *J* = 7.1, 1.4 Hz, 2 H, 3′), 7.39 (tt, *J* = 7.3, 1.5 Hz, 1 H, 4′), 6.25 (br s, 1 H, 1), 2.27 (s, 3 H, $CH_3$-C5). $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 145.4 (3), 143.8 (5), 130.4 (1′ phenyl), 128.7 (4′ phenyl), 128.6 (3′ phenyl), 127.4 (2′ phenyl), 92.8 (4), 11.3 (Me). MS (LR-APCI$^+$): *m/z* calcd for $C_{10}H_9BrN_2$: 236.0; found: 236.8 [M + H]$^+$, 238.8 [M + 2 + H]$^+$.

**General Procedure for Preparation of Pyrazoles 7, 14a and 21a–o by Oxidation of Pyrazolines 13 and 20a–p with Oxygen**

A solution of pyrazoline HCl salt **20** or **13** (2 mmol) in DMSO (10 mL) under 1 atm of pure $O_2$ gas was heated at 85 °C for 1–2 h or until the consumption of the starting material. The reaction solution was cooled to ambient temperature and poured into water (200 mL) with stirring to afford a suspension. The suspension was stirred at ambient temperature for 1 h, and solids were collected by filtration and washing with water. The solids were dried under vacuum at 45 °C overnight to afford pyrazoles **7**, **14a**, and **21**.

**Analytical Data for Pyrazole 7**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 13.33 und 13.00 (br s, NH two tautomers), 7.61–7.67 (m, 4 H, 2′, 3′, 5′, and 6′ phenyl), 4.55 (s, 2 H, 4), 3.63 (t, *J* = 5.7 Hz, 2 H, 7), 2.85–2.91 (m, 5 H, $MeSO_2$, and 6). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 142.37 (3), 141.21 (7a), 135.17 (1′ phenyl), 129.74 (q, *J* = 32.6 Hz, 4′ phenyl), 126.41 (2′ and 6′ phenyl), 125.85 (q, *J* = 3.9 Hz, 3′ and 5′ phenyl), 124.10 (q, *J* = 287.5 Hz, $CF_3$), 109.61 (3a), 43.09 (4), 42.86 (6), 36.93 ($MeSO_2$), 22.77 (7). $^{19}$F NMR (282 MHz, $CDCl_3$): δ = –62.60. MS (LR-APCI$^+$): *m/z* calcd for $C_{14}H_{14}F_3N_3O_2S$: 345.1; found: 346.1 [M + H]$^+$.

**Analytical Data for Pyrazoline 13**

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 7.87 (s, 2′, 3′ 5′, and 6′phenyl), 4.80 (br d, *J* = 10.27 Hz, 1 H, 3), 3.91 4.07 (m, 2 H, 4 and 6), 3.62–3.78 (m, 1 H, 3a), 3.08 (br t, *J* = 11.65 Hz, 1 H, 4), 3.01 (s, 3 H, $MeSO_2$), 2.85–3.01 (m, 2 H, 6), 2.65–2.79 (m, 2 H, 7). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 172.67 (7a), 138.98 (br s, 1′ phenyl), 130.01 (q, *J* = 31.7 Hz, 3′ and 5′ phenyl), 129.95 (2′ and 6′ phenyl), 126.90 (q, *J* = 3.3 Hz, 3′ and 5′ phenyl), 124.49 (q, *J* = 272.6 Hz, $CF_3$), 63.54 (3), 51.92 (3a), 49.01 (4), 44.82 (6), 37.34 ($MeSO_2$), 27.96 (7). MS (LR-APCI$^+$): *m/z* calcd for $C_{14}H_{16}N_3O_2S$: 347.1; found: 348.1 [M + H]$^+$; titration $Cl^-$: calcd for $C_{14}H_{16}N_3O_2S$·HCl: 9.25%; found: 9.79%.

(16) Detailed procedures along with full analytical data are available in the Supporting Information.

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