A New Reagent to Access Methyl Sulfones

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Dedicated to the people of Ukraine

Abstract. A new chemical reagent to access methyl sulfones has been developed. Its reaction with various *bis*-nucleophiles leads to the rapid formation of previously unknown heteroaromatic methyl sulfones. Analogous strategy can also be used to construct alkyl-, CHF_2-, CF_3- and even bicyclo[1.1.1]pentane-containing derivatives. These compounds have been demonstrated to have a high potential for use in medicinal chemistry and coordination chemistry.

Introduction

Methyl sulfone ($MeSO_2$) is a standard polar substituent used in chemistry together with methoxy, dimethylamino, acetoxy, and acetyl (Figure 1). It is common in agrochemicals,[1] and can be found in structures of >30 drugs.[2,3] All of them are either aliphatic or aromatic compounds (Figure 1, see also SI p. S6-S7). Heteroaromatic methyl sulfones, due to the lack of convenient and effective chemical approaches to them, are considerably much less investigated.

Two common approaches to heteroaromatic methyl sulfones exit. Both routes rely on the modification of the already installed functional groups: (a) oxidation of the thiomethyl group;[4] and (b) metal-mediated cross-coupling of halides/boronates with sodium sulfinate[5,6] or sulphur dioxide/methyl iodide (Figure 1).[7,8,9,10,11]

Here, we present a principally novel approach to methyl sulfones that relies on the 1,3-heterocycle disconnection logic with the newly developed reagent **1** (Figure 1).

Results and discussion

Background. In our daily practice, we often use two standard approaches to methyl sulfones described above (Figure 1). Recently, we received a request from a pharmaceutical company for a synthesis of pyrazole **2** (Scheme 1), which was described in a patent before.[12] In that method, bromide **3** was treated first with *n*BuLi followed by the addition of $(MeS)_2$. "*Due to its smell, the crude product* (**4**) *was used in the next oxidation reaction without further purification*." Oxidation of the latter with *m*CPBA gave 51 mg of the needed product **2** in 26% yield after a column chromatographic separation. It became obvious to us, that a principally novel approach to pyrazole **2** was needed. We decided to challenge the preparation of a new reagent with the already installed $MeSO_2$-substituent that could be easily converted into the needed product.

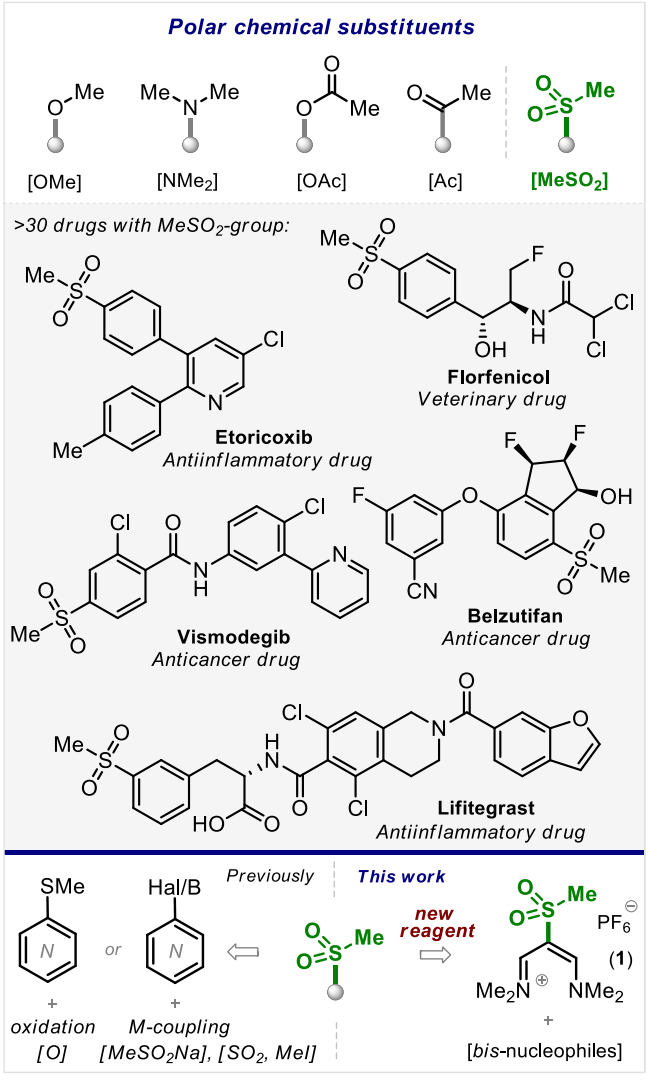
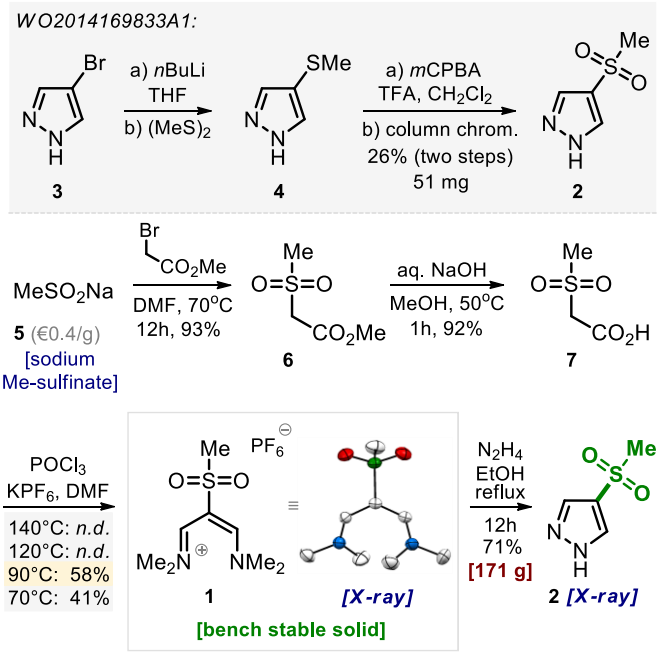


Figure 1. $MeSO_2$-substituent: state-of-the-art.

New reagent. Having studied the literature, we brought our attention to vinamidinium salts that are used to access substituted (hetero)aromatic compounds via a 1,3-disconnection logic.[13] In 1961, *Arnold* obtained 2-chlorovinamidinium perchlorate by reaction of chloroacetic acid under Vilsmeier-Haack conditions.[14] Later, *Gupton* and others extended this approach to obtain various vinamidinium perchlorates.[15] In 2000, *Davies* and colleagues developed safer vinamidinium hexafluorophosphate salts.[16]

Keeping this in mind, we decided to attempt the preparation of the previously unknown $MeSO_2$-vinamidinium reagent **1** (Figure 1). At the beginning, we were concerned that the activated methyl sulfone substituent would not be compatible with the harsh Vilsmeier-Haack conditions, but out of curiosity still decided to pursue that route. From the commercially available and inexpensive sodium methyl sulfinate, we first obtained ester **6** (Scheme 1). The subsequent saponification afforded the carboxylic acid **7**. As we previously envisioned, the first experiments at the Vilsmeier-Haack reaction of acid **7** failed. At high temperatures (120-140 °C), the formation of the unidentified complex mixtures was observed, presumably due to the undesired reactions at the activated $MeSO_2$-group. Varying the reaction conditions, however, revealed that performing the reaction at 90 °C allowed isolation of the desired compound **1** in 58% yield. Decreasing the reaction temperature further led to a reduction of the reaction yield. Compound **1** was a yellow crystalline solid stable at room temperature in air for at least one year. The structure of reagent **1** was confirmed by X-ray crystallographic analysis.[17]



Scheme 1. $MeSO_2$-pyrazole **2**: patent approach *vs* this work. X-ray crystal structure of compound **1** (carbon – white, oxygen – red, nitrogen – blue, sulphur - green). Hydrogen atoms and PF_6^- anion are omitted for clarity. Ellipsoids are shown at a 30% probability level.

The subsequent reaction of reagent **1** with hydrazine hydrate in EtOH under reflux smoothly gave the desired pyrazole **2** (Schemes 1, 2). Importantly, using this approach, we could easily obtain the product in 171 g amount in a single run. Its structure was confirmed by X-ray crystallographic analysis .[17]

Scope. Having finished the synthesis of pyrazole **2**, we wondered if reagent **1** could be used to assemble other $MeSO_2$-substituted heterocycles. First, we tried various *N*,*N*-*bis*-nucleophiles. Reaction with methyl hydrazine and functionalized aromatic hydrazines cleanly gave the corresponding pyrazoles **8**-**12** in 48-90% yield (Scheme 2). Reaction with guanidine, urea and thiourea led to the formation of pyrimidines **13**-**15** in 54-95% yield. Reaction with *S*-methyl thiourea, however, gave instead of the expected product **16**, the dimethylamino derivative **17**. The latter must have been formed via the initial formation of compound **16** and the subsequent SNAr-reaction with dimethylamine present in the reaction mixture. Reaction with substituted amidines gave pyrimidines **18**-**21** in 94-96% yield. Reaction of **1** with 2-chloroacetamide in pyridine gave instead of the expected product **22**, the corresponding pyridinium salt **23**. Cyclization of **1** with various amino *NH*-heterocycles produced bicyclic products **24**-**30**.

It is important to note that this method worked efficiently well on milligram, gram, and even multigram scales (**2**, **13**) without any significant change in the reaction yield. Most products were crystalline solids, and could be purified easily by crystallization. For liquid/oil compounds the purification was performed by column chromatography. The molecular structures of products **8**, **9**, **12** and **29** were confirmed by X-ray crystallographic analysis.[17]

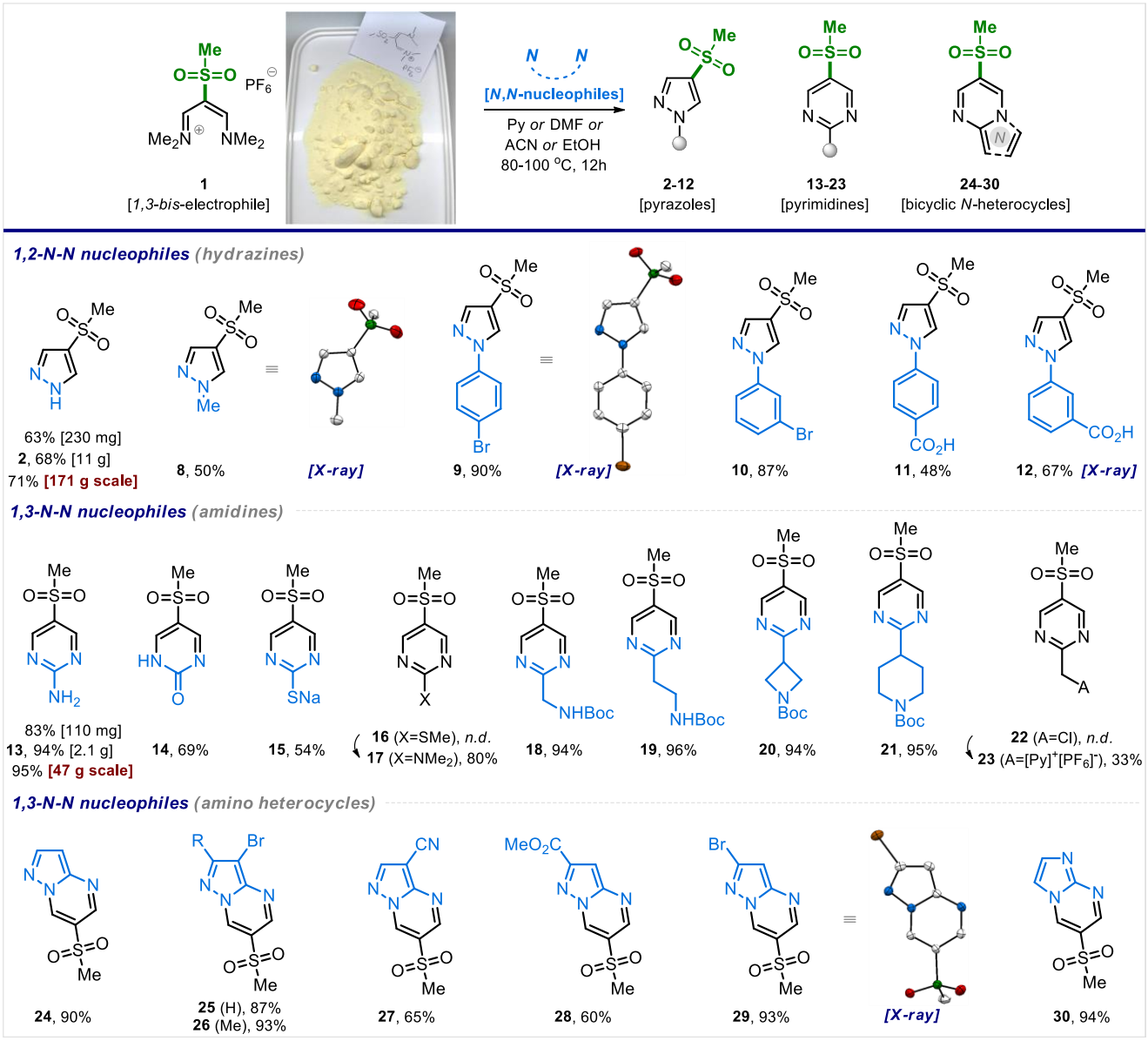
Next, we tried various *N,C-bis*-nucleophiles (Scheme 3). The reaction of vinamidinium salt **1** with glycine derivates gave pyrroles **31**-**33** in 49-95% yield. Analogously, pyridones **34**-**36** and pyridines **37**, **38** were synthesized in 46-92% yield. The reaction of salt **1** with various amino pyrazoles, amino isoxazoles, amino thiazoles, amino pyrroles, and amino thiophenes gave the corresponding bicyclic heterocycles **39**-**46** in 76-93% yield. It is worth noting that while the reaction of reagent **1** with methyl 5-amino-2-furoate in pyridine gave the desired bicyclic product **47**, the analogous reaction in acetonitrile led to the selective formation of the non-cyclized compound **48**. The reaction of **1** with electron-rich aminouracil, aminopyridine, and anilines gave bicyclic products **49**-**54** in 49-89% yield. The structure of compounds **34**, **41**, **42** and **45** was confirmed by X-ray crystallographic analysis.[17]

Remarkably, despite the simplicity of the current approach to methyl sulfones, the preparation of all compounds **8**-**54** has never been described before by any methods.

The developed method to $MeSO_2$-derivatives was not without limitations, however. It worked well only for the electron-rich systems. Not sufficiently activated *para*-bromo and *para*-methoxy anilines gave only the side products **55** and **56**, correspondingly. From reagent **1** we also could not obtain products **57**-**60** as formation of a complex mixtures was observed in each case (Scheme 3; see also SI p. S39-S40).

Modifications. Representative modifications of the resulting methyl sulfones were undertaken to obtain various functionalized building blocks (compounds with one or two functional groups) for use in medicinal chemistry (Scheme 4A). Saponification of the ester group in products **28**, **32**, **33**, **35** and **40** gave carboxylic acids "**a**". Acidic cleavage of *N*-Boc group in **18**-**21** gave amines "**b**". The reaction of pyrimidone **14** and pyridines **34**, **35** with $POCl_3$ afforded compounds with active chlorine atoms "**c**". Alkylation of compound **15** with methyl iodide gave the previously inaccessible product **16**. Finally, treatment of compound **50** with hydrobromic acid gave pyridone **50d**, and its subsequent reaction with $POCl_3$ afforded chloride **50e**.

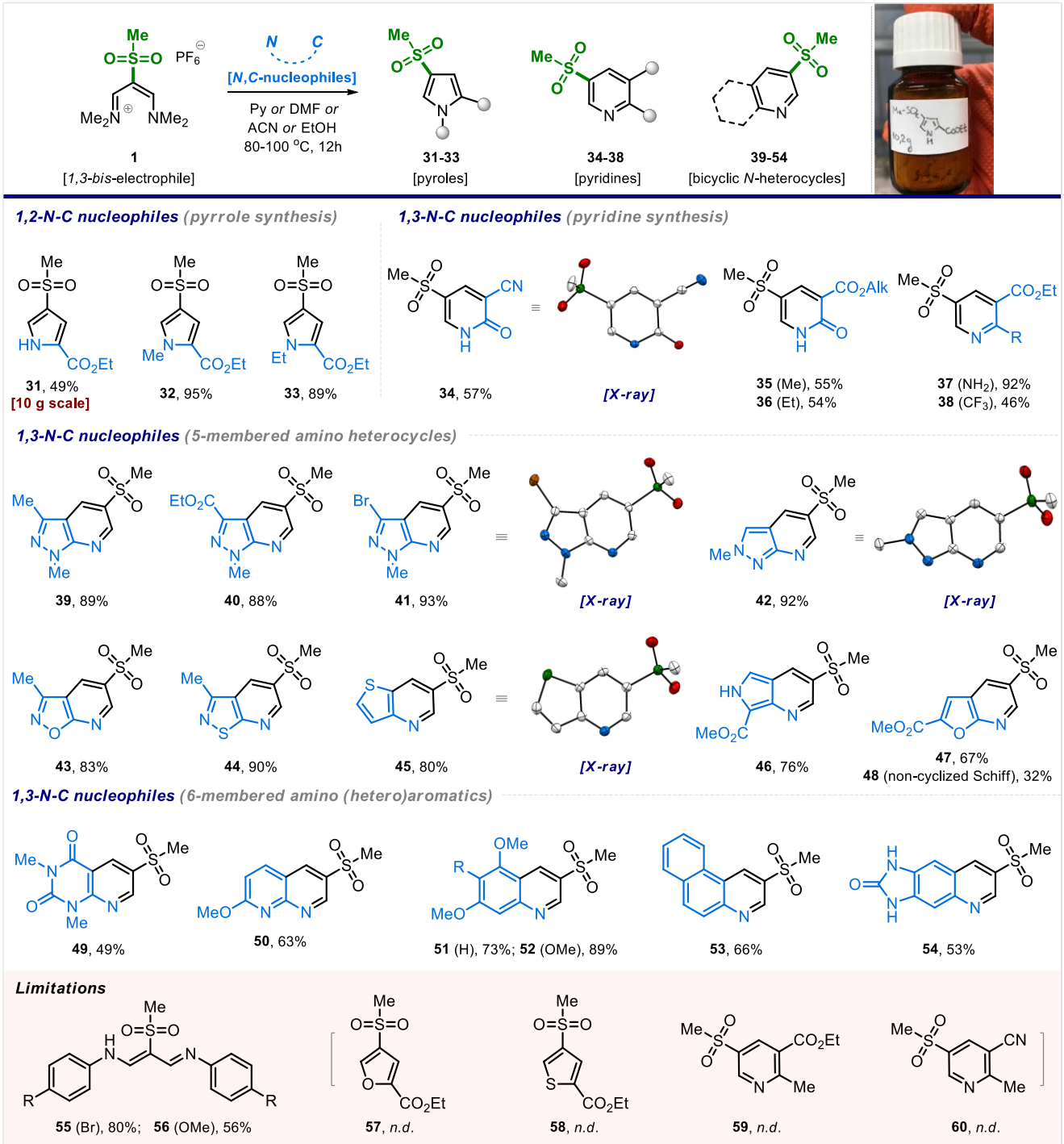
Alkyl sulfones. Having a practical and scalable procedure to reagent **1** in hand, we wondered if other alkyl sulfones could be obtained in a similar way. In fact, treatment of ethyl (**61**) and



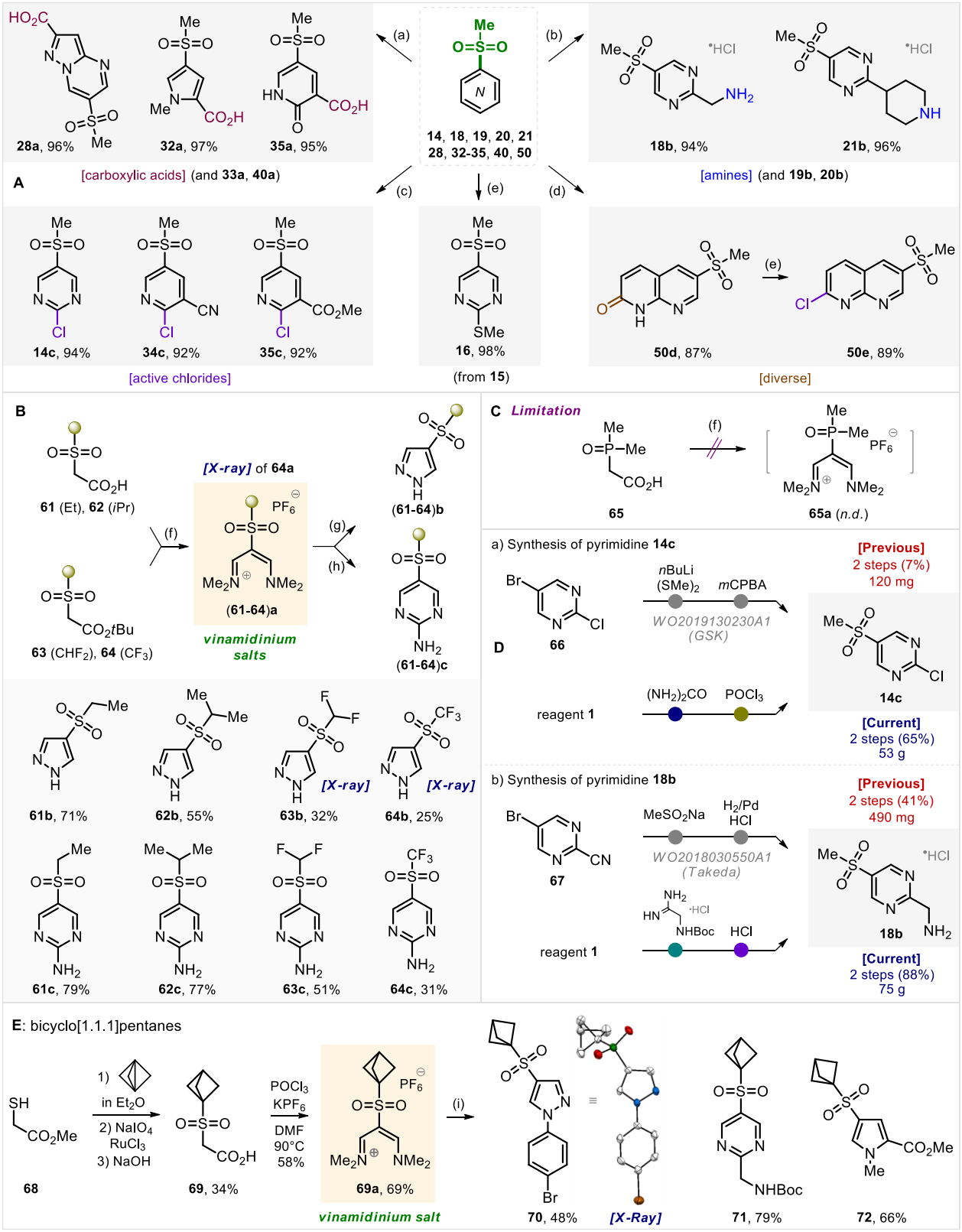
Scheme 2. *Reaction conditions:* compound **2**: N_2H_4·H_2O, EtOH, reflux, 12 h. Compound **8**: $MeNHNH_2$·H_2SO_4, K_2CO_3, DMF, 70 °C, 12 h. Compounds **9-12**: *N,N-bis*-nucleophiles, Py, 90 °C, 12 h. Compound **13**: guanidine acetate, K_2CO_3, MeCN, 60 °C, 12 h. Compound **14**: urea, K_2CO_3, Py, 100 °C, 12 h. Compound **15**: thiourea, NaOMe, MeOH, 50 °C, 12 h. The product was isolated as a sodium salt. Compound **17**: S-Me thiourea hydroiodide, Py, rt, 12 h (compound **17** was obtained instead of expected **16**). Compounds **18-30**: *N,N-bis*-nucleophiles, Py, 100 °C, 12 h. X-ray crystal structures of compounds **8** , **9** and **29** (carbon – white, oxygen – red, sulfur – green, bromine – orange, nitrogen - blue). Ellipsoids are shown at 30% probability level.

isopropyl (**62**) carboxylic acids (see SI p. 48 and 51) under Vilsmeier-Haack conditions gave the desired reagents **61a**, **62a** (Scheme 4B). For difluoromethyl- and trifluoromethyl-containing compounds, we discovered that the *tert*-butyl esters **63** and **64** could be directly converted in one step into the vinamidinium salts **63a**, **64a**. The reaction of all four reagents **61a**-**64a** with hydrazine hydrate gave pyrazoles **61b**-**64b** in 25-71% yield.[18] The treatment of reagents **61a**-**64a** with guanidine provided pyrimidines **61c**-**64c** in 31-79% yield. These two representative reactions of reagents **61a**-**64a** demonstrated that they could be widely used for the preparation of other sulfonylated derivatives similar to those obtained from reagent **1** (Schemes 3, 4). The molecular structures of compounds **63b**, **64a** and **64b** were confirmed by X-ray crystallographic analysis.[17]

Due to the discovery of the *Brigatinib* drug,[19] the P(O)Me_2-substituent has recently become popular in chemistry.[20] We, therefore, decided also to attempt the preparation of the corresponding vinamidinium salt (Scheme 4C). Unfortunately, the reaction of carboxylic acid **65** under the previously used conditions led to the formation of a complex mixture, rather than the desired reagent **65a**.



Scheme 3. *Reaction conditions*: compounds **31-47** and **49-56**: *N,N-bis*-nucleophiles, Py, 90 °C, 12 h; compound **48**: methyl 5-aminofuran-2-carboxylate, K_2CO_3, MeCN, 60 °C, 12 h. X-ray crystal structures of compounds **34**, **41**, **42** and **45** (carbon – white, oxygen – red, sulfur – green, bromine – orange, nitrogen - blue). Ellipsoids are shown at 30% probability level.



Scheme 4. Group A. *Reaction conditions:* (a) LiOH, MeOH, H_2O, rt, 12 h; (b) HCl in dry dioxane, rt, 12 h; c) $POCl_3$, reflux, 12 h; (d) i) 48% aq. solution of HBr, reflux, 12 h, ii) $POCl_3$, reflux, 12 h; (e) MeI, MeOH-H_2O, rt, 12h. Group B. *Reaction conditions*: (f) $POCl_3$, KPF_6, DMF, 90 °C, 2 h; (g) **61b-63b**: N_2H_4·H_2O, EtOH, reflux, 12 h; **64b**: N_2H_4·H_2O, MeONa, MeOH, 70 °C, 12 h; (h) guanidine acetate, Py, 100 °C, 12 h. Group D. Comparison of approaches to pyrimidines **14c** and **18b**. Group E. *Reaction conditions:* (i) *bis*-nucleophiles, Py, 90 °C, 12 h. X-ray crystal structure of compound **70** (carbon – white, oxygen – red, sulfur – green, bromine – orange, nitrogen - blue). Ellipsoids are shown at 30% probability level.

Comparison with other methods. The reagent **1** developed herein can be used not only to make new sulfones, but also to simplify the synthesis of the existing ones. The synthesis of pyrazole **2** was already discussed earlier (Scheme 1). Another example involves pyrimidine **14c**, which was reported in a patent. It was obtained in milligram quantities in 7% total yield from bromide **66** (Scheme 4D).[21] Using our method, pyrimidine **14c** could be obtained from reagent **1** in 53 g scale in a single run in 65% yield. Analogously, amine **18b** was obtained previously in 41% yield from the nitrile **67**.[22] Using reagent **1**, this product could be obtained in a multigram amount in one run in 88% yield (Scheme 4D).

Bicyclo[1.1.1]pentanes. Recently, bicyclo[1.1.1]pentanes were introduced as saturated bioisosteres of the benzene ring.[23] Therefore, novel methods to access these molecules are of importance. Recently, an approach towards bicyclo[1.1.1]pentane-containing sulfones bearing a halogen atom at the bridgehead position, Hal-[1.1.1]-SO_2R, was elaborated.[24] The reduction of the halogen atom in this system was problematic. Here, we have developed a reagent to synthesize the bridgehead non-substituted bicyclo[1.1.1]pentane sulfones: H-[1.1.1]-SO_2R. An addition of [1.1.1]-propellane to methyl thioglycolate (**68**) [25] followed by oxidation of the intermediate sulfide, and saponification of the ester group gave carboxylic acid **69**. The Vilsmeier-Haack reaction of the latter gave the expected reagent **69a** in 69% yield. Representative cyclizations of salt **69a** with various *bis*-nucleophiles gave bicyclo[1.1.1]pentane-containing pyrazole **70**, pyrimidine **71** and pyrrole **72**. The structure of compound **70** was confirmed by X-ray crystallographic analysis.[17]

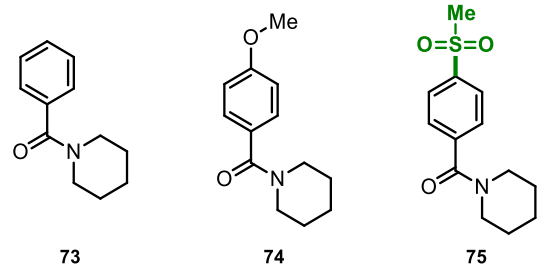
Physicochemical properties. Having developed a general and practical approach to methyl sulfones, we also decided to investigate the physicochemical properties of compounds with this substituent experimentally such as their lipophilicity, water solubility, and metabolic stability.

First, we synthesized three model amides **73**-**75** (see SI p. S65-S66; Figure 2) to see the impact of the replacement of the hydrogen atom (**73**) with the methoxy (**74**) and the methyl sulfone (**75**) groups at the lipophilicity. We used two parameters: calculated (clogP) [26] and experimental (logP) lipophilicities. According to both parameters, clogP and logP, replacement of the hydrogen atom (**73**) with the methoxy group (**74**) had a small effect at the lipophilicity. At the same time, an analogous replacement with the $MeSO_2$-substituent (**75**) led to a dramatic decrease of lipophilicity by ca. 1.2 logP units.

Next, we studied the physicochemical properties of antibacterial drugs *Sulfadiazine*, *Sulfameter*, and their $MeSO_2$-containing analog **76** (see SI p. S348-S368; Figure 2). All three compounds showed high solubility in water: 397 µM (*Sulfadiazine*) *vs* 361 µM (*Sulfameter*); 391 µM (**76**). All three compounds were also metabolically stable, outside the sensitivity range of the experimental method, CL_{int} (mg min^{-1} $µL^{-1}$): 0-2. Replacement of the hydrogen atom (*Sulfadiazine*) with the $MeSO_2$-substituent (**76**) also led to a dramatic decrease of the lipophilicity by ca. 1.2 clogP units: 0.39 (*Sulfadiazine*) *vs* -0.8 (**76**). An effect on the experimental lipophilicity, logD, was less pronounced, due to the values outside the senility range of the experimental method: -0.8 (*Sulfadiazine*) *vs* <-1 (**76**).

As a summary, in model compound **73**, and the antibacterial drug *Sulfadiazine*, the replacement of the hydrogen atom with the $MeSO_2$-substuent led to a dramatic decrease of lipophilicity by >1 logP/logD units.

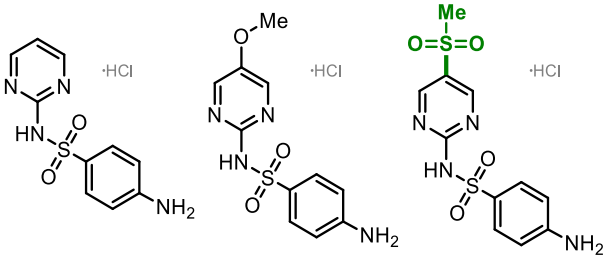
Model compounds



73 **74** **75**

Compound	*clogP*	*logP*
73	2.12	1.70
74	1.96	1.89
75	0.96	0.51

Analogs of drug



Sulfadiazine *Antibacterial drug* **Sulfameter** *Antibacterial drug* **76**

Compound	*Sol.*	*clogP*	*logD*	CL_{int}	$t_{1/2}$
Sulfadiazine	397	0.39	-0.8	2*	1073*
Sulfameter	361	0.23	-0.2	0*	7565*
76	391	-0.8	<-1	1*	1519*

Figure 2. Physicochemical properties of model compounds **73**-**75**; antibacterial drugs *Sulfadiazine* and *Sulfameter*, and $MeSO_2$-containing analog **76**. *Sol.*: the experimental kinetic solubility in phosphate-buffered saline, pH 7.4 (µM). *logP*: the experimental distribution coefficient in n-octanol/water. Reliable logP values could be obtained within a range of 1.0-3.0. *logD* (7.4): the experimental distribution coefficient in *n*-octanol/phosphate-buffered saline, pH 7.4. Reliable logD values could be obtained within a range of 1.0-4.5. *clogP*: the calculated lipophilicity. CL_{int}: the experimental metabolic stability in human liver microsomes (µL min^{-1} mg^{-1}). $t_{1/2}$ (min): the experimental half-time of a metabolic decomposition in human liver microsomes. *Parameter should be considered as approximate due to the high stability of compounds.

Application in coordination chemistry. Many of the *N*-heterocyclic compounds noted above could serve as good ligands for metal ions. To illustrate one such utility, pyrazolates of silver(I) were investigated, which represent an important class of compounds with interesting properties and useful applications.[27,28,29] They most commonly adopt planar structures featuring nine-membered Ag_3N_6 metallacycles[27-29] and often show various types of intertrimer argentophilic Ag…Ag contacts

leading to supramolecular aggregates.[30] Survey shows that silver complexes of 3,5-disubstituted pyrazoles are the most common,[27-29] while the homoleptic, binary silver complexes of 3,5-nonsubstituted pyrazoles are very limited.[31,32,33] Thus, we set out to probe the chemistry of pyrazoles **2** and **64b** with silver(I).

The treatment of a mixture of pyrazole **2** and $AgNO_3$ in methanol with triethylamine afforded {[**2**']Ag}$_3$ (**2**' = deprotonated **2**) as a white solid in 90% yield. Complex {[**64b**']Ag}$_3$ (**64b**' = deprotonated **64b**) was obtained from pyrazole **64b** analogously in methanol-acetonitrile mixture in 85% yield. These compounds were insoluble in dichloromethane, chloroform, toluene, benzene, and acetone, but somewhat soluble in tetrahydrofuran and dimethyl sulfoxide. Unfortunately, they did not provide crystalline material suitable for single crystal X-ray structure determination. Based on the literature analogy,[31,32] as well as mass spectroscopic data of {[**2**']Ag}$_3$ and {[**64b**']Ag}$_3$, we believe that they exist in the typical trinuclear form.[29]

In order to further confirm the identity of {[**2**']Ag}$_3$ and {[**64b**']Ag}$_3$, we prepared their phosphine complexes by treating their suspension with PPh_3 in dichloromethane. These reactions produced {[**2**']Ag(PPh_3)}$_2$ and {[**64b**']Ag(PPh_3)}$_2$, respectively, in essentially quantitative yield. They are air stable, white solids. Both complexes were soluble in common organic solvents allowing convenient characterization by multi-nuclear NMR spectroscopy, and recrystallizations to generate X-ray quality crystals.

X-ray crystallographic analyses revealed that they were dinuclear species (Figure 3; see SI p. S335-S345). These molecules sit on a center of inversion and the six-membered Ag_2N_4 cores adopt essentially planar configuration. For comparison, {[pyrazole]Ag(PPh_3)}$_2$ is dimeric and has a planar core.[34] The Ag-P distances of {[pyrazole]Ag(PPh_3)}$_2$, {[**2**']Ag(PPh_3)}$_2$ and {[**64b**']Ag(PPh_3)}$_2$ are all similar at 2.376(1), 2.3713(4), and 2.3703(3) Å, respectively, and do not show any effects of having a sulfonyl group on the ring backbone (see SI p. S335). The $^{31}P\{^1H\}$ NMR resonance of {[**2**']Ag(PPh_3)}$_2$ and {[**64b**']Ag(PPh_3)}$_2$ at room temperature have been observed at δ 11.3 and 13.8 ppm, respectively, which is marginally down-field from the chemical shift observed for {[pyrazole]Ag(PPh_3)}$_2$ (δ 9.87 ppm).[34]

Overall, $MeSO_2$- and CF_3SO_2-substituted pyrazoles afford silver complexes in excellent yields and could serve as useful ligand support for other metal ions.

Conclusions

In this work, we have developed a new chemical reagent **1** to access methyl sulfones. Its reaction with various *N,N*- and *N,C*-*bis*-nucleophiles leads to the formation of the previously unknown methyl sulfones. This transformation works efficiently on a milligram, gram and even multigram scale. Analogous strategy can also be used to construct alkyl-, CHF_2-, CF_3- and even bicyclo[1.1.1]pentane-containing derivatives. These compounds have been comprehensively characterized. They also have been demonstrated to have a high potential for use in medicinal chemistry and coordination chemistry.

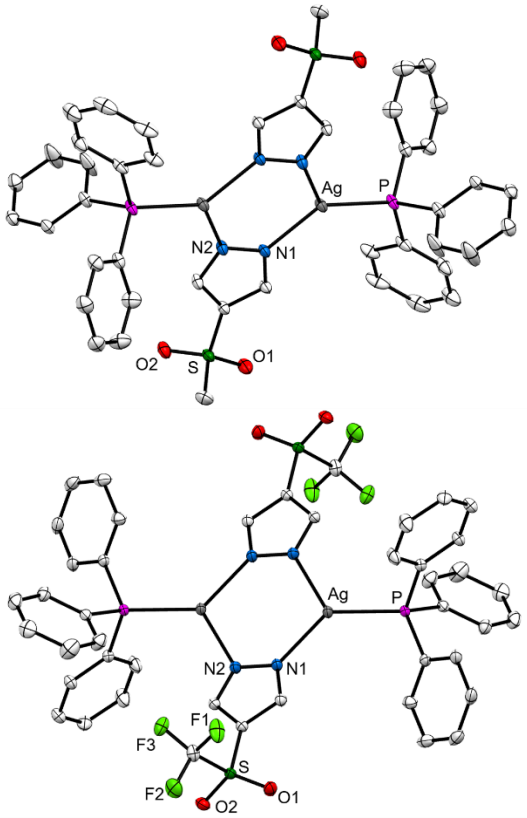


Figure 3. Molecular structures of {[**2**']Ag(PPh_3)}$_2$ and {[**64b**']Ag(PPh_3)}$_2$. Ellipsoids are shown at a 50% probability level. Hydrogen atoms have been omitted for clarity.

Acknowledgments

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Conflict of Interest

Some authors of this work are employees of a chemical supplier Enamine.

Data availability statement

The authors declare that data supporting the findings of this study are available within the paper and its supporting information.

Keywords: heterocycles; medicinal chemistry; methyl sulfone; bicyclo[1.1.1]pentane; fluorine.

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Graphical abstract

A new chemical reagent to access methyl sulfones has been developed. Its reaction with various *bis*-nucleophiles leads to the rapid formation of the previously unknown heteroaromatic methyl sulfones. Analogous strategy can also be used to construct alkyl-, CHF_2-, CF_3- and even bicyclo[1.1.1]pentane-containing derivatives. These compounds have been demonstrated to have a high potential for use in medicinal chemistry and coordination chemistry.