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Regioselective Synthesis of Sulfonylpyrazoles via Base Mediated Reaction of Diazosulfones with Nitroalkenes and a Facile Entry into Withasomnine‡

Rahul Kumar and Irishi N. N. Namboothiri*

Department of Chemistry, Indian Institute of Technology, Bombay, Mumbai 400 076, India

irishi@iitb.ac.in

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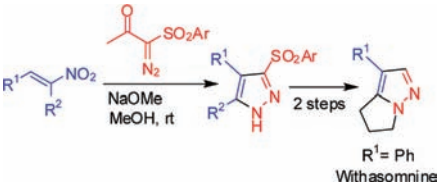
ABSTRACT



A base mediated reaction of α-diazo-β-ketosulfone with nitroalkenes affords sulfonylpyrazoles as single regioisomers in excellent yield in a one-pot room temperature reaction. Aryl, heteroaryl, styrenyl, alkyl, hydroxymethyl, and hydrazinyl groups could be introduced on the pyrazole ring by the appropriate choice of nitroalkenes. Synthesis of sulfonylpyrazole fused to other heterocycles and application of the methodology to an expedient synthesis of a pyrazole alkaloid, Withasomnine, are also reported.

Organosulfones occupy a unique niche in organic synthesis owing to their versatility as substrates and intermediates in numerous transformations.[1] The diverse reactivity of active methylene sulfones[2] and vinyl sulfones[3] has been extensively exploited in the synthesis of complex molecules including natural products.[4] The ability of the sulfonyl group to undergo facile removal has elevated its status to one of the most enviable groups in functional group manipulation.[5] In the biological arena, organosulfones function as antibacterial, antiparasitic, DNA cleaver, anti-HIV, antiviral, and antiandrogen agents.[6] The well-known drugs Bicalutamide (antiprostate cancer) and Dapsone (antileprosy) possess a sulfonyl group. A highly bioactive heterocycle pyrazole is an integral part of the

‡ Dedicated to Prof. Vishwakarma Singh on the occasion of his 60th birthday.

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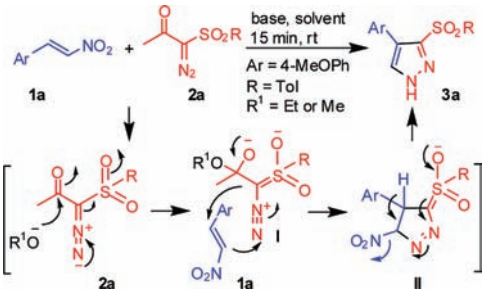
blockbuster drugs Celecoxib (antiarthritis), Viagra, and Thiomethisosildenafil (phosphodiesterase inhibitors). Applications of other pyrazole containing compounds as biological agents[7] and as ligands in coordination chemistry[8] are well-documented in the literature. For instance, Withasomnine, a pyrazole alkaloid, present in a medicinal plant, *Withania somnifera*, found in India and South Africa, exhibits analgesic and CNS depressant properties.[9] In spite of the above-mentioned significance of sulfone and pyrazole moieties, compounds containing a sulfonyl group directly attached to pyrazole received only limited attention.[10]

Recently, we reported a facile and regioselective synthesis of phosphonylpyrazoles via an alkoxide-mediated reaction of α-diazo-β-ketophosphonate, Bestmann−Ohira reagent (BOR),[11] with nitroalkenes and enones.[12] One-pot three component versions of our methodology[13] and extension of our methodology for the synthesis of pyrazole esters[14] were reported by others. We envisaged that α-diazo-β-ketosulfone would be an efficient S analog of BOR that would enable us to easily introduce a sulfonyl group to the pyrazole ring. Although α-diazo-β-ketosulfones have been employed in intramolecular cyclopropanation[15] and carbene insertion[16] reactions, surprisingly, their application as diazoalkane equivalents in cycloadditions for the synthesis of pyrazoles or pyrazolines remains unreported hitherto.

Table 1. Base Screening



entry	base[a]	solvent	% yield[b]
1	–	EtOH	no reaction
2	NaOEt	EtOH	61
3	KOH	EtOH	70
4	KOH	MeOH	62
5	NaOMe	MeOH	85
6	NaO-*t*-Bu	*t*-BuOH	intractable mixture

[a] 1.25 equiv. [b] Isolated yield after silica gel column chromatography.

The reaction conditions were optimized by treating *p*-methoxynitrostyrene **1a** with sulfone **2a** in the absence of any base and also in the presence of different bases and alcohols at room temperature (Table 1). No reaction in the absence of base (entry 1, Table 1) and formation of a complex mixture in the presence of a non-nucleophilic base such as NaO-*t*-Bu (entry 6, Table 1) confirmed that deacylation of **2a** by a nucleophilic base precedes cycloaddition in these cases as in the case of BOR[12] and also as in the concise mechanism shown in Table 1. Although the reaction was complete in about 15 min in all of the other cases, entries 2−5 indicate that NaOEt in EtOH (entry 2) and KOH in EtOH or MeOH (entries 3−4) were less efficient as compared to NaOMe in MeOH (entry 5, Table 1). Therefore, further reactions were conducted using NaOMe in MeOH at room temperature.

Under the above optimized conditions, various aromatic nitroalkenes **1a**−**k** were treated with sulfones **2a** and **2b** to afford sulfonylpyrazoles **3a**−**m** in good to excellent yields (Table 2). Comparison of entries 1 and 6 shows that there is no appreciable difference in the yield when sulfones **2a** and **2b** were used (Table 2). No major aromatic substituent effect is also observed on the yield or rate of reaction. For instance, nitrostyrenes possessing a strongly electron-donating substituent such as OMe (**1a** and **1f**−**h,** entries 1, 6, 8−10) and a strongly electron-withdrawing substituent such as NO_2 (**1i**−**k**, entries 11−13) provide the adducts in high yield (75−97%, Table 2). While increasing the number of strongly electron-donating substituents (OR)

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Table 2. Synthesis of Aryl Sulfonylpyrazoles **3** from β-Aryl Nitroethylenes **1** and Diazosulfone **2a** or **2b**

entry	Ar, **1**	**2**	pyrazole **3**	% yield[a]
1	4-OMePh, **1a**	**2a**	**3a**	85
2	Ph, **1b**	**2a**	**3b**	90
3	4-ClPh, **1c**	**2a**	**3c**	84
4	3-BrPh, **1d**	**2a**	**3d**	97
5	4-CH_3Ph, **1e**	**2a**	**3e**	81
6	4-OMePh, **1a**	**2b**	**3f**	89
7	Ph, **1b**	**2b**	**3g**	92
8	3,4-$(OMe)_2$Ph, **1f**	**2b**	**3h**	82
9	3,4,5-$(OMe)_3$Ph, **1g**	**2b**	**3i**	84
10	benzo[*d*][1,3]dioxole, **1h**	**2b**	**3j**	75
11	2-NO_2Ph, **1i**	**2b**	**3k**	97
12	3-NO_2Ph, **1j**	**2b**	**3l**	82
13	4-NO_2Ph, **1k**	**2b**	**3m**	94

[a] Isolated yield after purification by silica gel column chromatography.

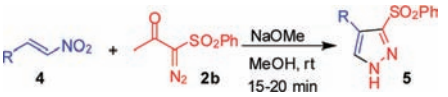
marginally lowers the yield (entries 6, 8−10), a strongly electron-withdrawing group (NO_2) at the ortho or para position as compared to meta has a positive effect (entries 11−13, Table 2). Parent nitrostyrene **1b** (entries 2 and 7) and nitrostyrenes possessing weakly electron-donating substituents **1c**−**1e** (entries 3−5) also deliver the corresponding sulfonylpyrazoles **3b**, **3g**, and **3c**−**e**, respectively, in excellent yield (Table 2).

Subsequently, nitroethylenes with diverse β-substituents **4a**−**f** were treated with sulfone **2b**, under the above conditions, to afford pyrazoles **5a**−**f** in good to high yields (Table 3). These include β-heteroaryl nitroethylenes **4a** and **4b** (entries 1−2), β-alkyl nitroethylene **4c** (entry 3), and a push−pull system such as β-aminonitroethylene **4d** (entry 4, Table 3). It may be noted that nitrodienes **4e** and **4f** also react with **2b** to afford the corresponding sulfonylpyrazoles **5e**−**f** in good to high yields (entries 5−6, Table 3).

Having successfully synthesized a variety sulfonylpyrazoles **3** and **5** by treating various β-substituted nitroethylenes **1** and **4** with sulfones **2a**−**b** under our mild and simple experimental conditions, we proceeded to synthesize 3,4,5-trisubstituted pyrazoles **7** by employing α,β-disubstituted nitroethylenes **6** (Table 4). Although less impressive yields and longer reaction times were encountered in these cases, we were pleased to isolate the 3,4,5-trisubstituted pyrazoles **7a**−**e** (entries 1−5, Table 4).

Furthering the scope of our methodology was explored by treating nitroethylene that is part of a heterocycle such

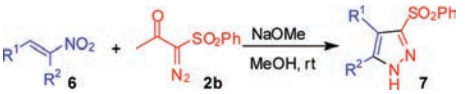
Table 3. Synthesis of Heteroaryl and Alkyl Pyrazoles **5** from β-Heteroaryl and Alkyl Nitroethylenes **4** and Diazosulfone **2b**



entry	R, **4**	pyrazole **5**	% yield[a]
1	2-Furyl, **4a**	**5a**	78
2	2-Thienyl, **4b**	**5b**	69
3	Cyclohexyl, **4c**	**5c**	70
4	Morpholino, **4d**	**5d**	80
5	PhCH=CH, **4e**	**5e**	74
6	*o*-OMePhCH=CH, **4f**	**5f**	83

[a] Isolated yield after purification by silica gel column chromatography.

Table 4. Synthesis of 3,4,5-Trisubstituted Pyrazoles **7** from α,β-Disubstituted Nitroethylenes **6** and Diazosulfone **2b**



entry	R^1	R^2	**7**	time (h)	% yield[a]
1	Ph	Me	**7a**	24	62
2	2-Furyl	Me	**7b**	24	69
3	4-MeOPh	CH_2OH	**7c**	0.5	77
4	2-Furyl	NENHE[b]	**7d**	0.5	83
5	$(CH_2)_4$		**7e**	0.5	61

[a] Isolated yield after purification by silica gel column chromatography. [b] E = CO_2Et.

as **8** with sulfone **2b** aimed at synthesizing a sulfonylpyrazole moiety fused to other heterocycles **9** (Scheme 1). Thus, nitrochromenes **8a** and **8b** reacted with sulfone **2b** in the presence NaOMe/MeOH to afford sulfonylpyrazoles **9a**−**b** in nearly quantitative yields within 1 h at room temperature.

Scheme 1. Synthesis of Fused Sulfonylpyrazoles **9** from Nitrochromenes **8**

Due to the potent biological properties of Withasomnine,[9] the possibility of developing a general and efficient route to its total synthesis via application of our methodology appeared attractive. The approaches reported in the literature involve intramolecular alkylation,[17] oxidative coupling,[18] conversion of cyclopropanols to pyrazoles,[19]

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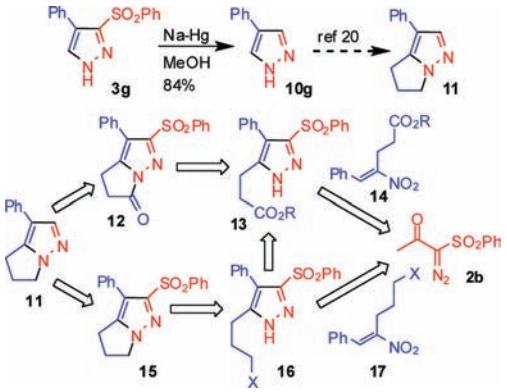
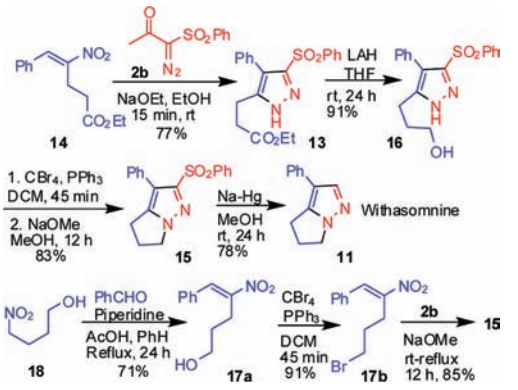
Scheme 2. Synthetic Approaches to Withasomnine **11**



Scheme 3. Total synthesis of Withasomnine **11**



radical cyclization,[20,21] sydnone cycloaddition,[22] multicomponent coupling,[23] and hydrazine-1,3-dicarbonyl cyclization.[24] Indeed, smooth desulfonation of **3g** to **10g** in our hands and the procedure available in the literature for the transformation of **10g** to Withasomnine **11** via N-alkylation and intramolecular radical cyclization[20] confirmed that **3g** per se is a good intermediate for the synthesis of **11**. However, we wished to develop novel and efficient routes to **11** and felt that **11** would be accessible via carbonyl reduction and desulfonation of lactam **12** which in turn would arise via intramolecular cyclization of ester **13** (Scheme 2). Synthesis of **13** could be achieved by our methodology by reacting diazosulfone **2b** with nitroester **14**. An alternative strategy to synthesize **11** would be via **15**, the intramolecular cyclization product of **16** which in turn would arise from reaction of **2b** with **17** under our experimental conditions.

Initially, we prepared nitroester **14** via a Rauhut–Currier type reaction of β-nitrostyrene with ethyl acrylate,[25] or via a high yielding condensation of ethyl 4-nitrobutyrate with benzaldehyde.[26] 1,3-Dipolar cycloaddition of nitroester **14** with sulfone **2b** under our conditions (NaOEt, EtOH) afforded pyrazole ester **13** in 77% yield (Scheme 3). Reduction of the ester group in **13**[27] with LAH afforded corresponding alcohol **16** in 91% yield which was transformed through a one-pot reaction involving bromination and intramolecular cyclization to the Withasomnine precursor **15** in 83% yield. Finally, desulfonation of **15** to Withasomnine **11** was achieved in 78% yield using Na–Hg in MeOH.

An alternative route developed for the synthesis of **15** involved condensation of nitrobutanol **18**[28] with benzaldehyde to afford nitroalcohol **17a** in 71% yield. Conversion of alcohol **17a** to bromide **17b** in 91% yield followed by cycloaddition of **17b** with sulfone **2b** furnished sulfonyl Withasomnine **15**.

Besides the simplicity and efficiency of our strategy,[29] synthesis of other natural and non-natural analogs of Withasomnine **11** is an attractive prospect which will be pursued and reported in due course.

In conclusion, a one-pot regioselective method has been developed for the synthesis of sulfonylpyrazoles from diazosulfones and nitroalkenes under very mild and simple experimental conditions.[30] The scope of the method has been demonstrated by synthesizing a variety of functionalized and fused pyrazoles. Our methodology has been successfully employed for the total synthesis of a pyrazole alkaloid Withasomnine.

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Supporting Information Available. Complete characterization data and copies of NMR spectra for all of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Attempted transformation of **13** to cyclized product **12** (Scheme 2) in the presence of excess base and/or under reflux conditions led to a complex mixture presumably due to transesterification, hydrolysis, etc.

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(29) The overall yields in our two approaches (Scheme 3) are 23% and 25%, respectively. These compare well with those of the reported approaches, viz. 27% in the radical cyclization method in which commercially available bromopyrazole was used directly (ref 20) and 24% in the multicomponent coupling method (ref 23).

(30) The regiochemistry of the sulfonylpyrazoles was confirmed from ^{1}H–^{1}H NOE observed in a representative system **5c** between cyclohexyl protons and the aromatic protons (see the SI) and also from synthesis of Withasomnine **11** from nitroalkene derivatives **14** and **17a**.