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Metal-free, Base Promoted sp^2 C-H Functionalization in Sulfonamidation of 1,4-Naphthoquinones

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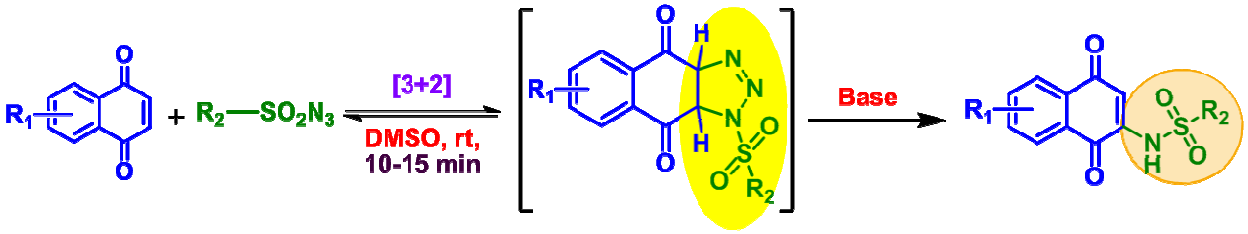
Abstract:

A novel metal-free, base catalysed sp^2 C-H functionalization in the sulfonyl amidation of 1,4-naphthoquinones via a [3+2] cycloaddition reaction using sulfonyl azides under mild reaction conditions is reported. In this straightforward, atom- and step-economical protocol, the active alkene moiety of quinone undergoes a thermal azide-alkene [3+2] cycloaddition followed by proton abstraction, ring opening and elimination of nitrogen molecule to form the sulfonamidation products in good yield and all the synthesized sulfonamidation derivatives exhibit good absorption and emission characteristics. In addition, the electrochemical properties of both 1,4-naphthoquinone and menadione sulfonamidation derivatives are studied and significant redox potentials are observed. Other important features of this methodology are readily accessible and easy to handle starting materials, milder conditions, reaction with a wide range of substrates and shorter reaction times with good yields.



Key words:

- Metal-Free
- [3+2]-cycloaddition
- No by-products
- Room-temperature reaction
- Short-reaction time
- Significant absorption, emission and electrochemical properties

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Introduction

Carbon–carbon and carbon-heteroatom bond formation by direct functionalization of carbon–hydrogen bonds of organic compounds has recently emerged as a powerful method.[1] Due to the ubiquitous nature of C−H functionalities in almost every molecular scaffold, the C−H bond activation represents a "hot" topic.[2] Among the various C−H bond activations, the C−H bond amination allows the conversion of low-cost products, such as simple hydrocarbons, active alkenes and aromatic compounds into high added-value nitrogen-containing derivatives such as natural products, pharmaceutical drugs and functional materials.[1,2] This dual C–H/N–H activation[3,4] technique has received tremendous attraction in recent years, since the enormous synthetic potential required for this class of organic transformations and selective C-N bond formation[5] is still a major challenge for organic chemists and the wide range of catalytic systems developed for catalytic C−H amination bears testimony to the importance of this C−H functionalization reaction. Transition metal catalyzed amination of aryl (pseudo) halides with amines or amides involving a combination of suitable ligands under basic conditions with the stoichiometric amount of metal catalysts has been developed under various conditions.[3-5] However, this procedure generates stoichiometric amounts of byproducts such as hydrogen halides or their base salts. Direct amination reactions of arenes in the presence of external oxidants[6] too generates the stoichiometric amount of byproducts.

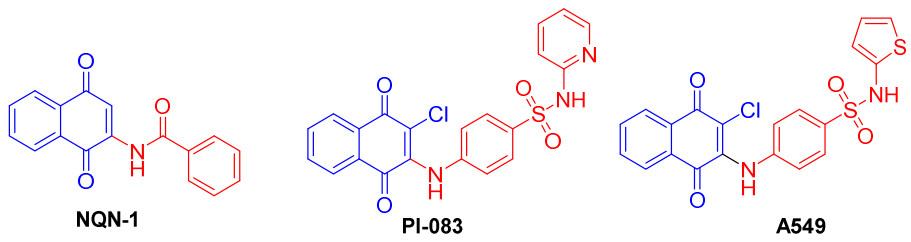

Fig 1. Representative examples of anti-cancer drugs based on 1,4-naphthoquinone and sulfonamide moieties.[10]

The arylsulfonamide moiety is an important functional group with significant pharmaceutical activity and plays a vital role as a structural design motif in medicinal chemistry, in cancer chemotherapy (Fig. 1), diuretics and hypoglycemia. Apart from their commercialized applications as antibacterial/antibiotic agents, sulfonamides are also

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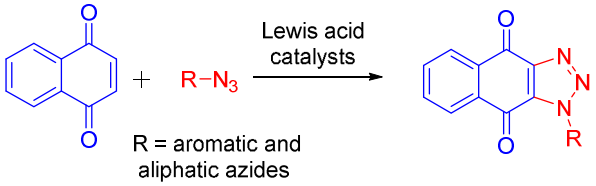
known to inhibit several enzymes such as carbonic anhydrase, cysteine protease, HIV protease and cyclooxygenase.[7-9]

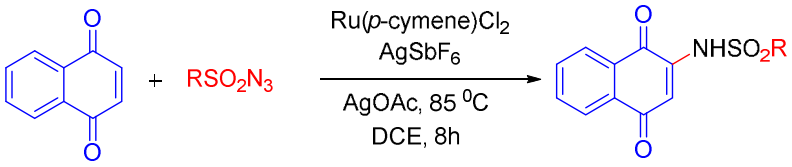
Naphthoquinones are privileged molecular scaffolds in medicinal chemistry due to their unique redox properties. They serve as vital links in the electron transport chains in the metabolic pathways and participate in multiple biological oxidative processes. The redox cycling of quinones present in many natural products with important biological activities may be initiated by either a one- or two-electron reduction.[11] Quinones are both oxidants and electrophiles, and the relative contributions of these properties to both their toxic and therapeutic activities are influenced by their chemical structure and the substituent effects in the quinone nucleus. The quinone moiety in many drugs such as mitoxantrone, ametantrone and doxorubicin show potent antitumor activity and have been used as effective classes of anticancer agents and recently our group have reported a novel synthesis and anticancer activity of naphtho[2,1-*b*]furan-2,5-diones and benzo[*de*]chromene-2,6-diones obtained from 2- and 5-hydroxynaphthoquinones.[12]

Previous report:

a) Synthesis of naphtho[2,3-d][1,2,3]triazole-4,9-diones

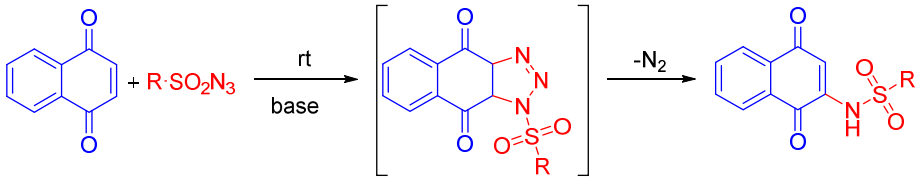


b) Sulfonamidation of 1,4-naphthoquinone using a Ruthenium catalyst



R= methyl, 85%
R= tolyl, 78%

Present work: *Metal-free sulfonamidation of 1,4-naphthoquinone*



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Recently, the groups of Chang[13] *and* Wang[14] have reported a synthesis of naphtho[2,3-*d*][1,2,3]triazole-4,9-dione derivatives *via* [3+2] cycloaddition reactions of 1,4-naphthoquinone with various aromatic and aliphatic azides using various Lewis acid catalysed harsher reaction conditions.[13-15] Reddy *et al.* have reported sulfonamidation of 1,4-naphthoquinone using sulfonyl azides in the presence of ruthenium catalyst.[16] In our previous works, sulfonyl azide was used as one of the starting materials for *N*-sulfonylketenimine formation. Hence it is planned to couple sulfonyl azide (as a dipole) with 1,4-naphthoquinone (dipolarophile) at room temperature in the presence of a base, as only a few compounds have been reported so far in these easily available and medicinally important sulfonamide derivatives, despite the observation that these sulfonamide derivatives show the good medicinal property. The observed results of the present metal-free base catalysed CH-functionalization/sulfonamidation of 1,4-naphthoquinones using sulfonyl azides are discussed below.

Results and Discussion

Initially, the reaction was studied using 1,4-naphthoquinone (**1**), *p*-toluenesulfonyl azide (**2a**) as starting materials, dimethyl sulfoxide as solvent and potassium carbonate as a base in ambient conditions. The starting materials were consumed completely within 10 minutes and afforded the sulfonyl amidation product namely, *N*-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)-4-ethylbenzenesulfonamide (**3a**) in good yield and its structure was confirmed unambiguously by NMR and HRMS-ESI analyses. The reaction conditions were optimized further with various bases and solvents. Among the various bases used, inorganic bases like sodium, potassium and cesium carbonate gave better yields within 10 minutes (Table 1, entries 1-3). Uses of other inorganic bases like NaOH and KOH gave only moderate yield and took longer time (30 min.) than other bases (Table 1, entries 4 and 5). Further, we have utilized several other organic bases, which failed to give the desired sulfonyl amidation product (Table 1, entries 6-10).

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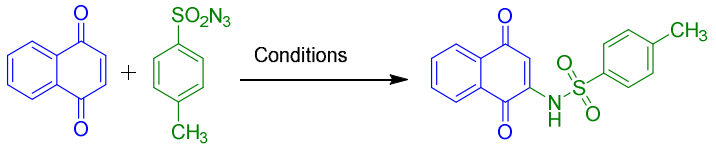
Table 1. Optimization of reaction conditions[a]



1 2a 3a

Entry	Solvent	Base	Time (min)	Yield (%)[b]
1	DMSO	K_2CO_3	10	66
2	DMSO	Na_2CO_3	10	63
3	DMSO	Cs_2CO_3	10	58
4	DMSO	NaOH	30	59
5	DMSO	KOH	30	53
6	DMSO	Pyrrolidine	10	-
7	DMSO	Morpholine	10	-
8	DMSO	Et_3N	10	-
9	DMSO	DIPEA	10	-
10	DMSO	Pyridine	120	-
11	DMSO	KSF mont.	120	-
12	DMSO	HT (5:1)	60	71
13	1,4-dioxane	K_2CO_3	120	-
14	THF	K_2CO_3	10	52
15	DMF	K_2CO_3	10	68
16	CH_2Cl_2	K_2CO_3	10	60
17	$CHCl_3$	K_2CO_3	10	62
18	CH_3CN	K_2CO_3	20	69
19	**DMSO**	**K_2CO_3**	**15**	**71**
20	DMSO	K_2CO_3	20	72
21[c]	DMSO	-	120	-
22[d]	DMSO	PTSA	120	-
23[e]	DMSO	HCl	120	-
24	DMSO	DBU	15	58

[a] **Reaction Conditions:** 1,4-Naphthoquinone (1.0 mmol), *p*-toluenesulfonyl azide (1. mmol), solvent 3.0 mL, base (1.2 0 mmol), rt; [b]Isolated yield; [c] Absence of base; [d] Presence of *p*-toluenesulfonic acid; [e]Presence of Hydrochloric acid.

In addition, we have also employed heterogeneous base catalysts HT (5:1) and KSF-montmorillonite. The reaction was slow in hydrotalcite (60 min.) but the yield was higher compared to other bases (Table 1, entry 12). In KSF, the reaction was very slow even after 120 minutes (Table 1, entry 11). In this type of sulfonyl amidation reaction, solvents played a crucial role. Among the various solvents, DMSO (71%) gave better

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yield compared to other solvents like 1,4-dioxane, THF, CH_2Cl_2, $CHCl_3$, CH_3CN and DMF,(table 1, entries 12-19). Further, the time variation study was also carried out in potassium carbonate as base and DMSO as a solvent. The reaction yield had increased (Table 1, entries 19 and 20) when the reaction time was increased from 10 to 15 and 20 minutes. Without the base, there was no reaction and this result indicated the importance of base in this sulfonamidation reaction (Table 1, entry 21). In addition, in the presence of acids like PTSA and HCl, the reaction did not proceed even after a long time (Table 2, entries 22 and 23). The reaction was also checked in the presence of DBU as a base. The reaction was found to be exothermic and the sulfonamidation product was obtained only in moderate yield (58%) (Table 2, entry 24).

With the optimized reaction conditions, the substrate scope of various active alkenes with various sulfonyl azides was explored utilizing various sulfonyl azides, substitutions like electron-donating, electron-withdrawing groups, halogen-substituted, fused ring and non-aromatic systems (**Table 2).**

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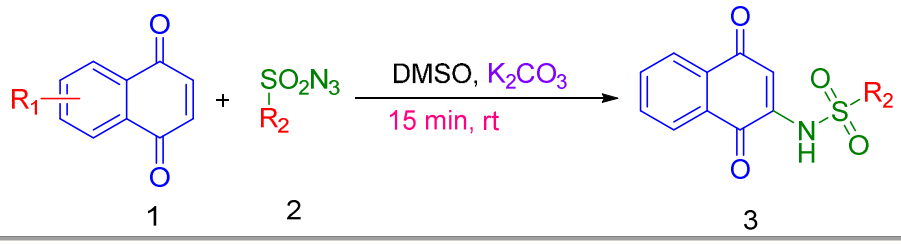
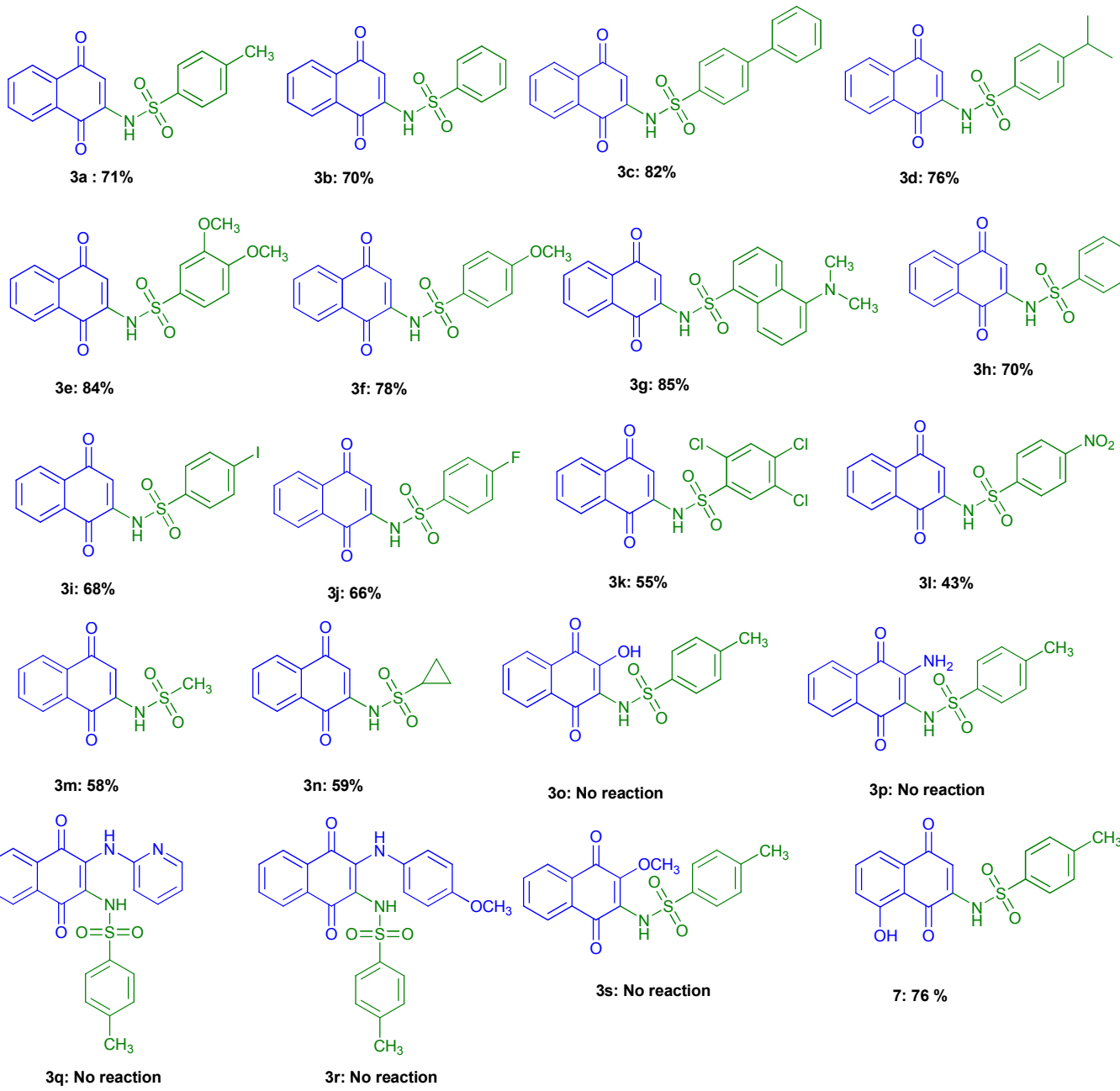
Table 2. Substrate scope in sulfonamidation of 1,4-naphthoquinone[a]





[a]**Reaction conditions:** 1,4-Naphthoquinone (1.0 mmol), sulfonyl azide (1.0 mmol), potassium carbonate (1.2 mmol), DMSO (3.0 mL), rt, 15 minutes.

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Among them, all electron-donating and fused ring substituted sulfonyl azides such as methyl (3a-71%), methoxy (3e-84%, 3f-78%), isopropyl (3d-76%), biphenyl (3c-82%) and dansyl substituents (3g-85%) gave the corresponding sulfonyl amidation product in good to excellent yield. Among the electron-withdrawing ones, nitro (3l–43%), 2,4,5-trichloro (3k-55%), halogens, bromo (3h-70%), iodo (3i-68%) and non-aromatic, cyclopropyl (3n-59%) substitutions, halogen substituted benzenesulfonyl azides gave better yield. An aliphatic sulfonyl azide namely methanesulfonyl azide also gave (3m-58%) better yields.

Attempts were also made to synthesise various 2-substituted-1,4-naphthoquinones, like 2-hydroxy-1,4-naphthoquinone, 2-amino-1,4-naphthoquinone, 2-((4-methoxyphenyl)amino)naphthalene-1,4-dione and 2-(pyridin-2-yl amino)naphthalene-1,4-dione. However, despite our best efforts, the expected sulfonamidation products were not formed. This is attributed to the resonance interaction between the hydroxyl group and amino group with the double bond in basic conditions which decreases the double bond character of naphthoquinone, making it less reactive towards sulfonyl azides (**Table 2, 3o-3r**). In a similar reaction with 2-methoxy-1,4-naphthoquinone, it was observed that the starting material is consumed completely, but there was no formation of the expected sulfonamidation product (**Table 2, 3s**).

In addition, the reactivity of 5-hydroxy-1,4-naphthoquinone was also studied with tosyl azide in the presence of base. All the starting materials were consumed within half an hour and the sulfonamidation product (**7**) was formed regioselectively in 76% yield (**Table 2**).

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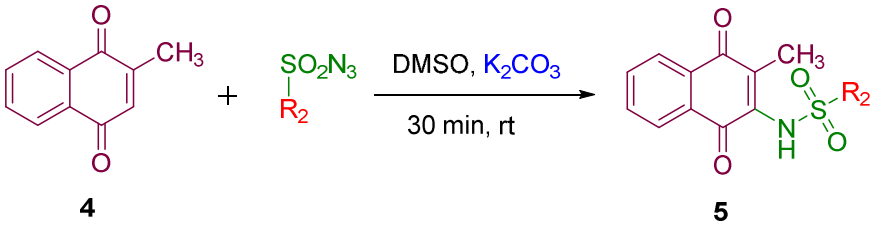
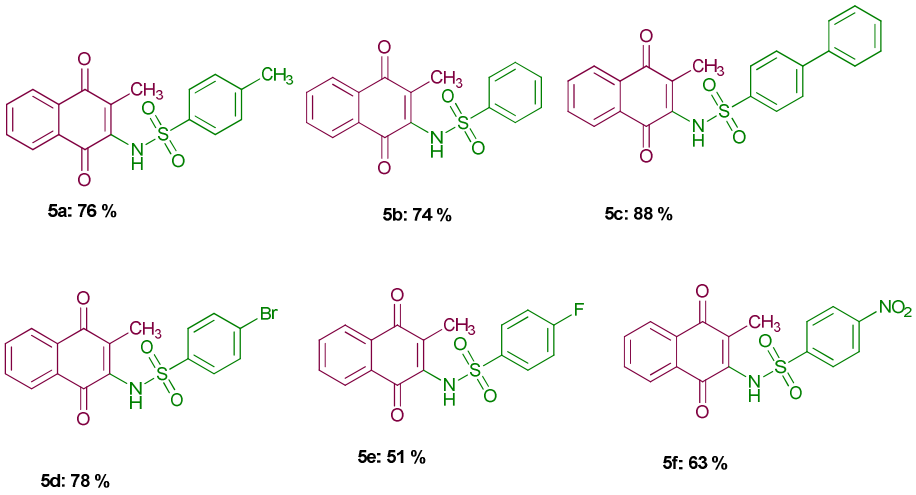
Table 3. Substrate scope in sulfonamidation of 2-methyl-1,4-naphthoquinone[a]





[a]**Reaction conditions;** 2-Methyl-1,4-naphthoquinone (1.0 mmol), sulfonyl azide (1.0 mmol), potassium carbonate (1.2 mmol), DMSO (3.0 mL), rt, 30 minutes.

Sulfonyl amidation reaction was also extended to a sterically hindered naphthoquinone, namely 2-methyl-1,4-naphthoquinone (menadione), instead of 1,4-naphthoquinone. Surprisingly, the same type of sulfonyl amidation product was observed in good yield but the reaction time had to be increased to 30 minutes. Due to the presence of methyl group in the 2nd position, the [3+2] cycloaddition reaction took place with a longer time. When the effect of substitutions in sulfonyl azide was studied, the same type of results was observed as in 1,4-naphthoquinone (**Table 3**). Electron-rich sulfonyl azides like 4-methyl (5a, 76%), 4-phenyl (5c, 88%) and 4-bromo (5d, 78%) substituted benzenesulfonyl azides gave better yields than unsubstituted (5b, 74%) and fluoro (5e, 51%) substituted benzenesulfonyl azides.

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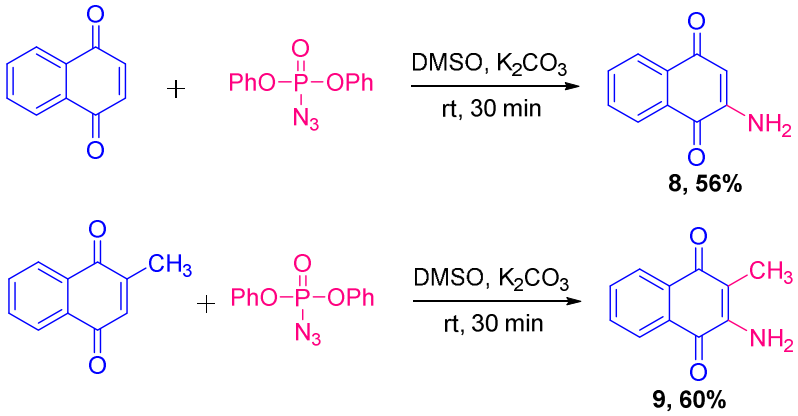
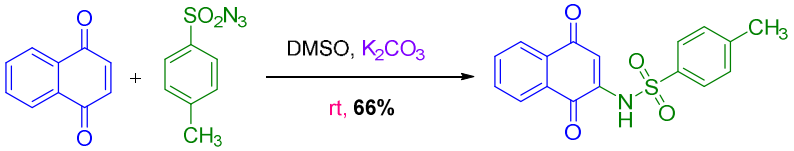


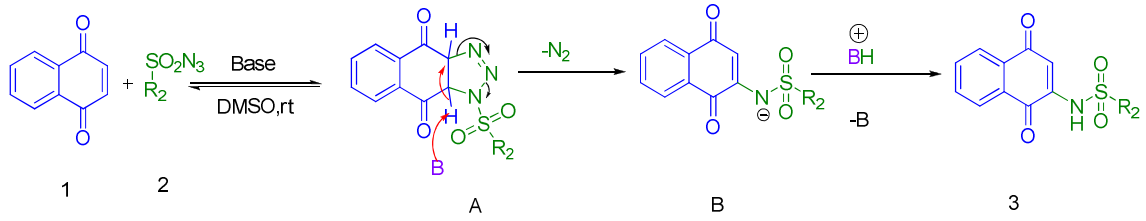
Scheme 1. Reaction of 1,4-naphthoquinones with diphenyl phosphoryl azide.

When diphenyl phosphoryl azide was used instead of sulfonyl azide to react with 1,4-naphthoquinone and 2-methyl-1,4-naphthoquinone under the same reaction conditions, the reaction is not successful and only the respective amines namely 2-amino-1,4-napththoquinone (**8, 56%**) and 2-amino-3-methyl-1,4-naphthoquinone (**9, 60%**) are obtained (**Scheme 1**). In addition, when the reaction was studied with other dipolarophile substrates like *p*-benzoquinone, flavone, dimethyl and diethylacetylene dicarboxylate (DMAD, DMED) and acrylonitrile with sulfonyl azide, the reaction was not successful even after 24hrs.



Scheme 2. Gram scale reaction for sulfonamidation of 1,4-naphthoquinone.

With industrial and biological applications in mind, gram scale reaction was also carried out using 1,4-naphthoquinone (5.0 mmol, 0.79 g), tosyl azide (5.0 mmol, 0.985 g), potassium carbonate (6.0 mmol, 0.830 g) and dimethyl sulfoxide (8.0 mL) in room temperature. The reaction gave selectively 66 % (1.08 g) of yield (Scheme 2).



Scheme 3. Plausible mechanism for sulfonamidation of 1,4-naphthoquinone.

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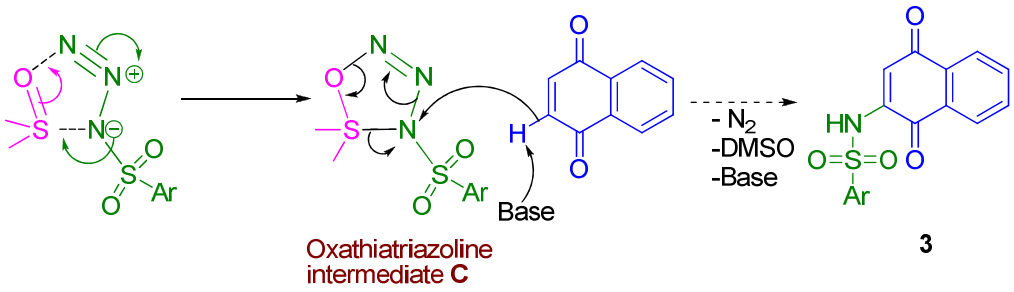
Based on the obtained experimental results, a plausible reaction mechanism was proposed (Scheme 3). In a major pathway, 1,4-naphthoquinone and sulfonyl azide undergo a thermal [3+2] cycloaddition, a thermodynamically favoured process,[17] to yield the cycloadduct (**A**). Since the ring opening reverse process is also thermally allowed, the somewhat less stable [3+2] adduct, formed in a particular percentage, undergoes irreversibly a base catalysed proton abstraction, ring opening and nitrogen extrusion reaction cascade, shifting the equilibrium in step 1 towards the adduct **3**.



Scheme 4. DMSO mediated minor pathway.

A subsequent minor pathway (Scheme 4) is also likely, involving interaction between DMSO (a good dipolarophile) and sulfonyl azide (a relatively sluggish 1,3-dipole) which may generate an oxathiatriazoline intermediate C,[18] which may react further with 1,4-naphthoquinone in the presence of base to yield the final product,.

Quinones are well known to participate in multiple biological oxidative processes due to their ability to generate reactive oxygen species. The fundamental feature of quinone is its ease of reduction, and hence its ability to act as an oxidizing agent. In folk medicine, plants containing naphthoquinones are often employed for the treatment of various diseases and several quinonoid derivatives isolated from traditional medicinal plants are being investigated for their anticancer properties.

Their electrochemical properties are also very important due to their bioreductive activation, either to semiquinone or to hydroquinone. There are several examples of correlations between electrochemical potentials and biological activities. For example, a definite correlation has been found between redox potentials and the inhibitory effects of naphthoquinones on Epstein–Barr virus early antigen activation and with their cytotoxicity. Another important significance of quinones in biological system is their one electron reduction, catalyzed by NADPH-cytochrome P450 reductase which yields

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unstable semiquinones. Quinones transfer electrons to molecular oxygen (O_2), and return to their original quinoidal formation, thus generating a superoxide anion radical (.O_2-). Superoxide can be converted to hydrogen peroxide (H_2O_2) via a superoxide dismutase (SOD)-catalysed reaction, followed by the formation of a hydroxyl radical (.HO) by the iron-catalyzed reduction of peroxide via the Fenton reaction. All of these highly reactive species may react directly with DNA or other cellular macromolecules, such as lipids and proteins, leading to cell damage.

Cyclic voltammetry investigations of quinones in the presence of oxygen in aprotic media have been considered as an useful tool for studying the interaction of oxygen and the superoxide anion radical with quinones and their radical anions. Both their toxic and therapeutic activities were influenced by their chemical structure, particularly substituent effects and the characteristics of the quinone nucleus. These unique features prompted us to study the photophysical and redox properties of the synthesized molecules in aqueous solution.

The absorbance and emission properties of sulfonylamidation products of both 1,4-naphthoquinone (331 nm) and 2-methyl-1,4-naphthoquinone (menadione, 332 nm) derivatives (**Figs. 2 and 3**) are studied in DMSO solution ($1x10^{-4}$ M). The sulfonamidation products of 1,4-naphthoquinone, exhibited a weak absorbance maximum in the region of 455 to 488 nm, ascribed to the intramolecular charge-transfer process (ICT) from the sulfonamido group to the 1,4-naphthoquinone core and emission at 540 to 603 nm (Fig. 2). All the molecules, except **3g**, show dual emission. While the shorter wavelength emission band is due to the localized emission, the longer emission is attributed to the twisted intramolecular charge transfer (TICT). In **3g**, three emission bands, are observed due to the presence of dansyl groups.

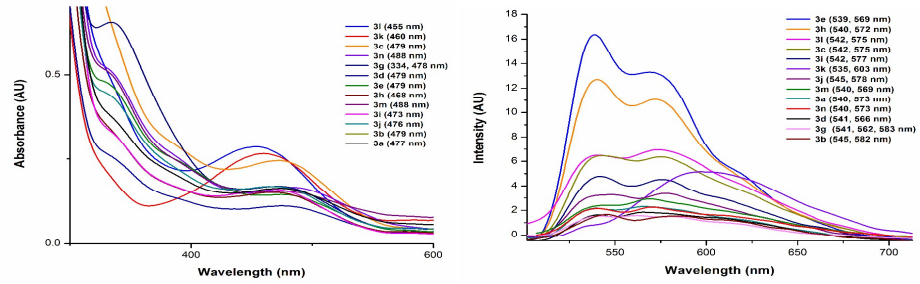

Fig.2 Absorbance and PL spectrum of (**3a-3n**)

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Menadione sulfonamidation derivatives also exhibit absorbance in the visible range of 485 to 506 and emission at 560 to 598 nm (Fig. 3). In this case also, except 5d and 5e, all the compounds show dual emission but the halogen-substituted sulfonamides 5d and 5e show the broad emission spectrum. Compared to menadione and 1,4-naphthoquinone, menadione sulfonamidation derivatives have shown higher absorbance and emission values.

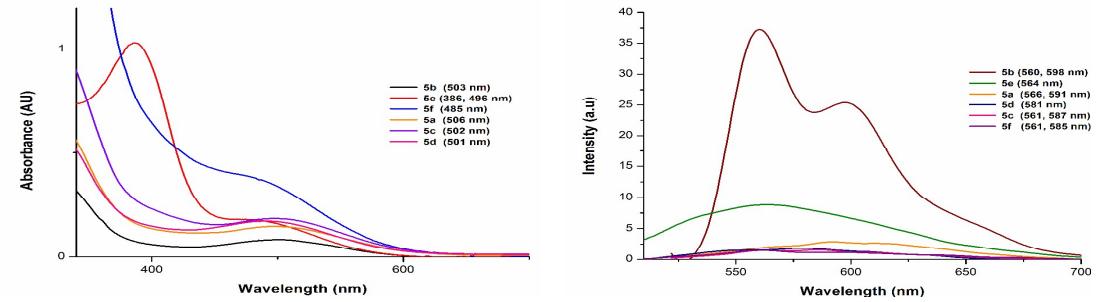

Fig.3 Absorbance and PL spectrum of (**5a-5f**)

In view of the potential redox properties of the naphthoquinone moiety in multiple biological oxidative processes[19] in nature, the electrochemical properties of the synthesized sulfonamidation products of 1,4-naphthoquinone and menadione (**Fig.4**) are also evaluated. In aprotic solvents, the reduction of sulfonamidation derivatives occurs through three successive one-electron transfers for all the derivatives except 1,4-naphthoquinone, which shows two successive one-electron transfers. The radical anion intermediate 1,4- $NQ^{-\cdot}$ formed in first one-electron transfer, $E_{Pc}1$ is subsequently reduced to quinone dianion 1,4-NQ^{2-} in a second $E_{pc}2$ step. Compared to both the starting materials 1,4-naphthoquinone and menadione, their sulfonamidation products show interesting modifications in redox properties. While the first redox wave is reduced more (with weaker current intensity), the second redox wave in weakly reduced (with equal current intensity). Another interesting feature is a larger value of $E_{1/2}$ for the first redox wave and lower value of $E_{1/2}$ for the second redox wave.

In addition to the two quasi-reversible steps, a third redox wave (broad and ill-defined cathodic and anodic peaks) at more negative potential is observed for the

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sulfonamidation products, which is likely the result of the reduction of the sulfonamide moiety to afford its radical anion.

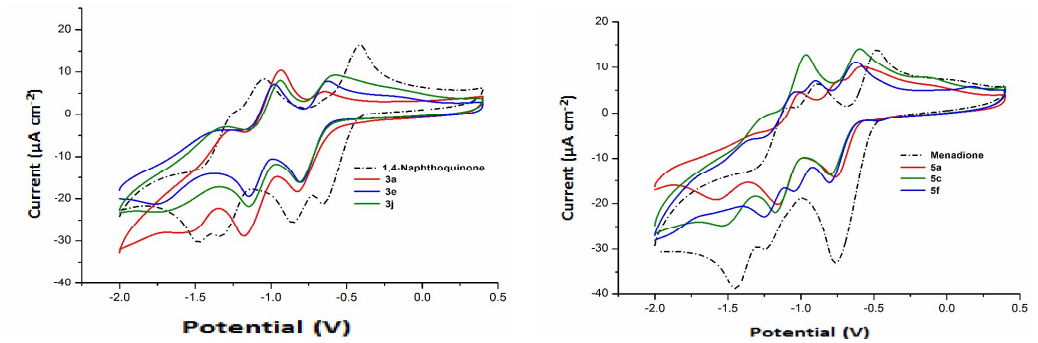

Fig. 4 Cyclic voltammogram of 1,4-napnthoquinone and menadione sulfonamidation derivatives in selective.

Conclusions

A novel synthetic protocol for sp^2C-H functionalization/sulfonamidation is developed *via* base-promoted [3+2] cycloaddition of 1,4-naphthoquinones and sulfonyl azides to synthesize sulfonamides. For the first time, this type of sp^2 C-H functionalization/sulfonamidation reactions is reported *via* [3+2] cycloaddition using sulfonyl azides. A variety of sulfonamides are prepared in moderate to excellent yields within a short reaction time. This method utilizes inexpensive and readily available reagents, simple experimental procedure, generates non-toxic by-products (N_2), demonstrates good functional group compatibility and proves to be versatile for a range of sulfonyl azides and various types of active alkenes such as 1,4-naphthoquinone and 2-methyl-1,4-naphthoquinone. A suitable mechanism is proposed. All the sulfonamidation derivatives of 1,4-naphthoquinone and menadione exhibit good absorption, emission properties and compared to the starting materials both sulfonamidation products shows good redox potential values.

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