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ARTICLE

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Metal free synthesis of 1-azaspiro[4.4]nonane-3-one system via reactions of nitrones with 1,1-disubstituted allenes

U. Amrutha[1] | Beneesh P.Babu[2] | Sreedharan Prathapan[1]

[1]Department of Applied Chemistry, Cochin University of Science and Technology, Kochi, Kerala, India

[2]Department of Chemistry, National Institute of Technology Karnataka, Surathkal, India

Correspondence
S. Prathapan, Department of Applied Chemistry, Cochin University of Science and Technology, Kochi 682022, Kerala, India.
Email: prathapan@cusat.ac.in

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Abstract

In the cycloaddition reaction between fluorenone *N*-aryl nitrones and 1,1-disubstituted allenes, the initially formed cycloadduct underwent facile [1,3] shift to give 1′-phenylspiro[fluorene-9,2′-pyrrolidin]-4′-ones. Although 1′-phenylspiro[fluorene-9,2′-pyrrolidin]-4′-ones are stable in solid state, a few of them underwent facile aerial oxidation in solution to give the corresponding 1′-phenylspiro[fluorene-9,2′-pyrrolidine]-4′,5′-diones in excellent overall yields.

1 | INTRODUCTION

Spiroheterocyclics such as spiropyrrolidinones are important structural motifs in biologically active compounds and organic materials [1,2]. Because of these valuable properties, synthesis of spiroheterocycles has attracted wide attention. Some of alkaloids which contain spiroheterocyclic ring having medicinal properties is given in Figure 1. In principle, 1,3-dipolar cycloaddition reactions can be adopted for the synthesis of spiroheterocyclics as well. Nitrones participate in 1,3-dipolar cycloaddition with alkenes, alkynes, and cumulenes to give several types of heterocyclic compounds such as isoxazolines, isoxazolidines, oxazolines, 1,2-oxazines, pyrrolidines, quinolones, indoles, dipyrromethanes etc. [3] Although reactions between nitrones and cumulenes are well documented, cycloaddition reactions between nitrones and allenes remains relatively less explored [4]. Available reports on nitrone-allene cycloadditions reveal diverse reactivity patterns including both concerted cycloaddition and stepwise reaction sequences [5]. Blechert and coworkers, for example, reported the synthesis of 2-vinylindoles by the reaction of *N*-aryl nitrones with electron-deficient allenes involving a domino sequence of cycloaddition, Cope rearrangement, retro-Michael addition, and indolization steps [5a]. Later Padwa reported that the reaction of *N*-aryl nitrones with activated allenes could form a benzazepin-4-one ring system via dipolar cycloaddition. Padwa's reaction sequence was similar to that of Blechert, ie, the reaction proceeds through an isoxazolidine cycloadduct which undergoes homolytic N—O bond cleavage and further cyclization to give a benzazepine ring system which on hydrolysis or retro-Mannich reaction affords indole derivatives [5b–m]. However, alternate mechanisms involving [1,3] and [3,3] sigmatropic shifts on initially formed products can also be proposed to account for the generation of these unexpected products. Subsequently, Anderson and coworkers described the synthesis of 1,4-enaminoketones by nucleophilic addition of *N*-alkenyl nitrones to electron-deficient allenes followed by [3,3] shift [6]. The synthesized 1,4-enaminoketones can be hydrolyzed to give substituted pyrroles. Anderson's

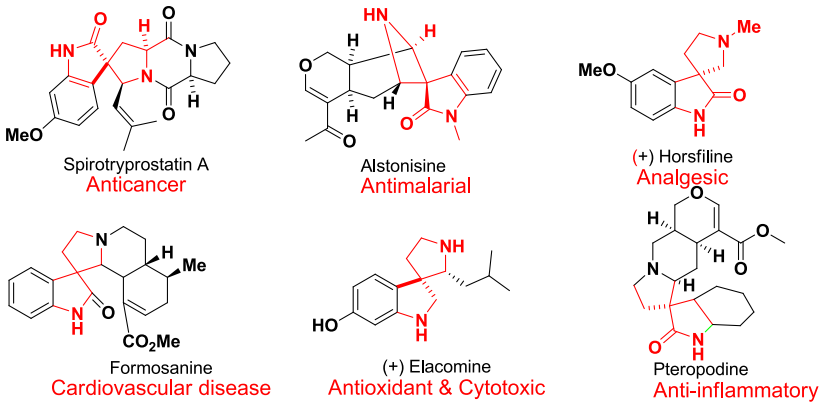
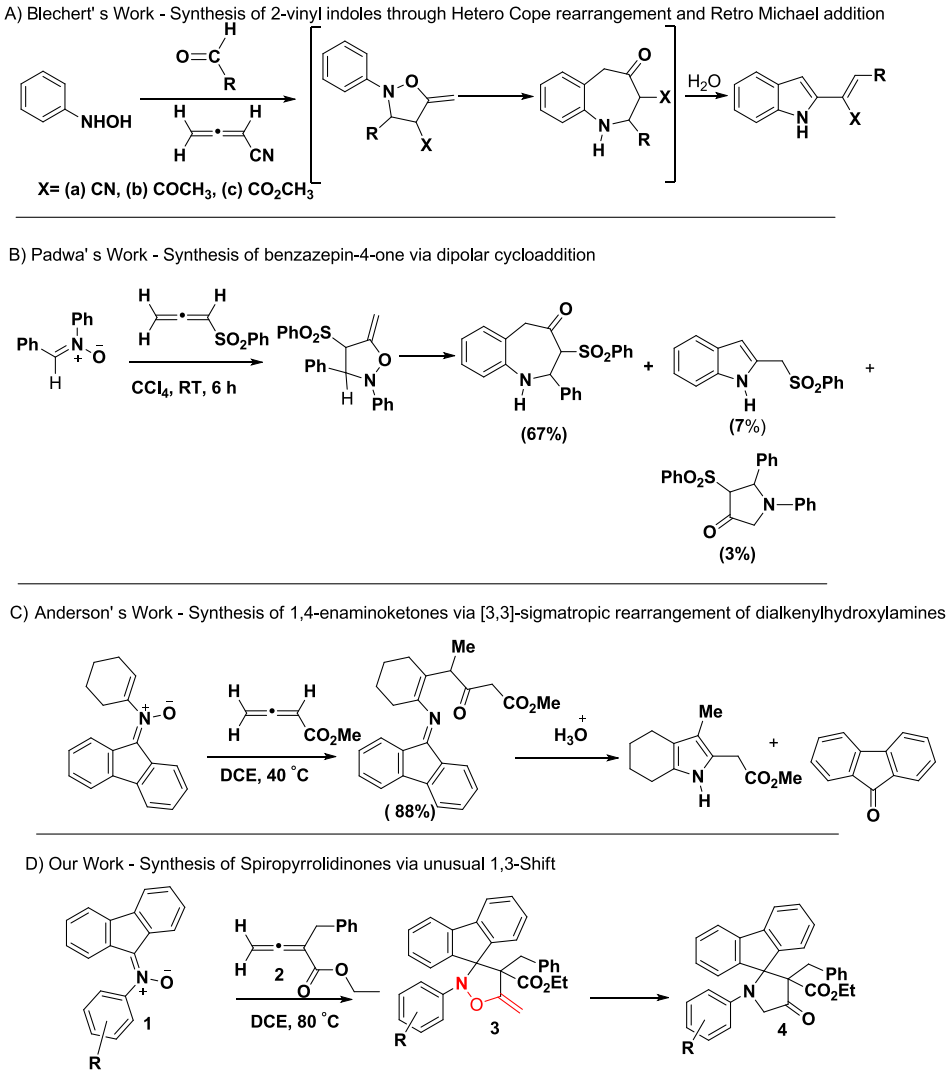


FIGURE 1 Alkaloids containing spiroheterocyclic ring [Color figure can be viewed at wileyonlinelibrary.com]

finding is significant since she demonstrated that nitrones undergo not only cycloaddition but also nucleophilic addition to dipolarophiles (Scheme 1). Meanwhile, we demonstrated Michael-type addition of *N*-aryl nitrones to electron-deficient acetylenes as a key step in the synthesis of highly substituted quinoline and indole derivatives [7]. Furthermore, we demonstrated that, depending on the nitrone used, the initially formed Michael adduct could undergo either [3,3] sigmatropic rearrangement or ring closure to give the formal isoxazoline cycloadduct. With nucleophilic adducts generated from aldonitrones, ring closure is favored while those from ketonitrones favored [3,3] sigmatropic rearrangement alluding to the role of steric factors in controlling selectivity. In this context, we

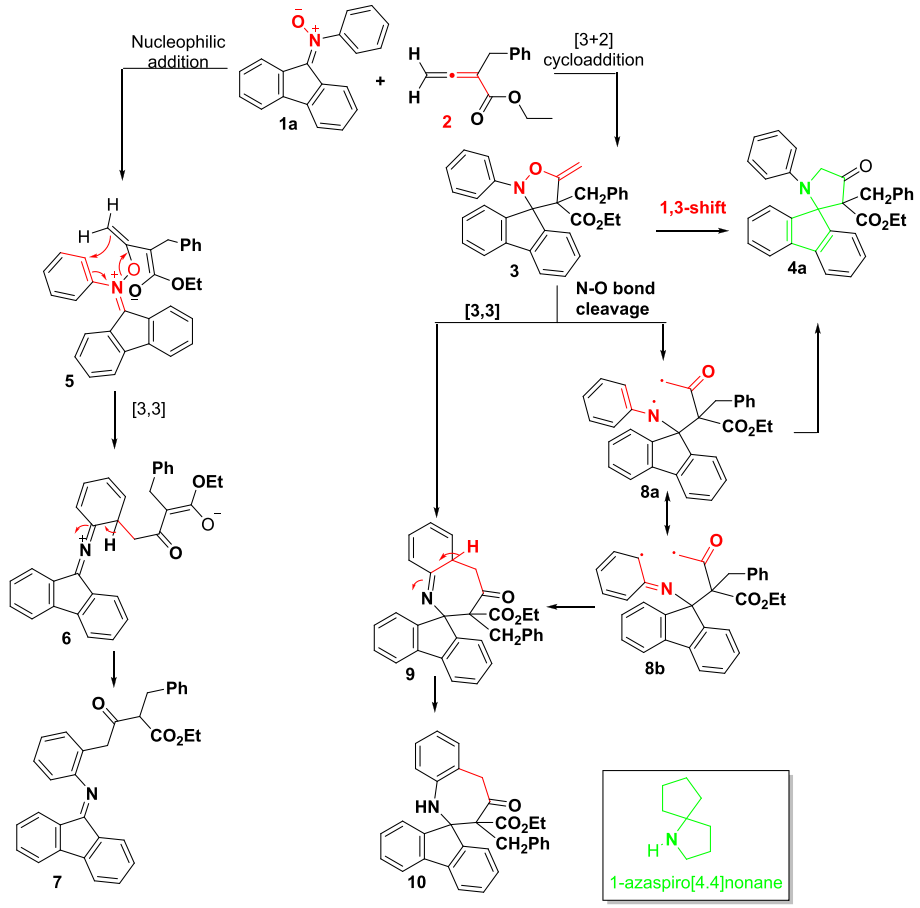


SCHEME 1 Diverse reactions between allenes and nitrones [Color figure can be viewed at wileyonlinelibrary.com]

explored the reaction between sterically crowded ketonitrone **1** and electron-deficient 1,1-disubstituted allene **2**. Our primary goals were to explore the mechanism of the reaction in greater detail and to probe alternate reaction possibilities between two versatile reagents: nitrones and allenes. En route, we developed an efficient, metal-free synthesis of spirofluorenylpyrrolidine-3-ones and their oxidation to spirofluorenylpyrrolidine-2,3-diones in good yields.

2 | RESULTS AND DISCUSSION

Nitrones **1a-l** [8a] and allene **2** [8g] were prepared by known procedures. Normal cycloaddition between **1** and **2** is expected to give highly substituted 1-azaspiro[4.4]nonane derivatives. In order to exploit this possibility, we investigated the reaction between **1** and **2** under different conditions. In the reaction between an equimolar mixture of **1** and **2** in dichloromethane (DCM) at room temperature, a new product identified as a 1:1 adduct by LC-MS analysis was formed in low yields. A slight improvement in product yield was observed upon prolonged heating in refluxing DCM. The product was separated by column chromatography over silica gel, and analytical quality samples and diffraction quality crystals were obtained by careful recrystallization from deaerated ethanol (vide infra). Based on available reports on nitrone-allene reactions, four different structures including (a) normal cycloadduct **3**, (b) imine **7** formed by nucleophilic addition followed by a [3,3]-sigmatropic shift analogous to that reported by Anderson, (c) **10** formed either by N—O bond heterolysis and recyclization from **3** as reported by Padwa or through a [3,3] sigmatropic shift from **3**, and (d) **4** formed either by N—O bond heterolysis and recyclization from **3** or a [1,3] shift in **3** (Scheme 2) are attributable to the new product. The absence of a prominent NH stretching frequency in the IR spectrum of adduct partially ruled out structure **10**. Both **7** and **10** are labile toward acidic hydrolysis leading to indole derivatives [5,6]. However, the new product obtained by us resisted hydrolysis even under strongly acidic conditions. Thus, we ruled out **7** and **10** as possible structures for the adduct leaving **3** and **4** as the most possible structures. We carefully examined spectral data to distinguish between these two isomeric structures. Closer examination of the IR spectrum of the product indicated the presence of an additional carbonyl group appearing at 1721 cm^{-1}, identified as a keto-



SCHEME 2 Possible structures and mechanism for the expected product [Color figure can be viewed at wileyonlinelibrary.com]

carbonyl on the basis of a signal appearing at δ 204 ppm in its ^{13}C NMR spectrum, indicating possible rearrangement of the initially formed cycloadduct **3**. In the ^{1}H NMR spectrum of the product, peaks attributable to the exocyclic methylene group were absent. Instead, two signals attributable to diastereotopic protons of an additional methylene group were observed at δ 4.70 and 4.57 ppm. DEPT analysis was also consistent with the presence of two saturated methylene carbons. These results clearly ruled out **3** as the product formed in this reaction. So, we propose **4** as the most probable candidate. The structure of the product was unequivocally identified as **4** on the basis of single crystal X-ray analysis (Figure 2).

Since 1-azaspiro[4,4]nonane skeleton present in **4** is a useful synthetic target present in several *cephalotaxus* alkaloids [9], we turned our attention to optimization of reaction conditions to maximize product yield and selectivity. To this end, we screened several solvents of varying polarity and boiling points. Based on our experience with the reaction between anthracenemethanamines and electron-deficient acetylenes [10], we anticipated possible solvent effects on the reaction between nitrones and allenes. Nucleophilic addition reported by Anderson is more likely to occur in polar solvents. Cycloaddition is more probable in nonpolar solvents, while N—O bond homolysis leading to radical processes reported by Padwa et al may be favored at higher temperatures. With these possibilities in mind, we repeated the reaction between **1** and **2** in solvents such as dichloroethane, *t*-butanol, cyclohexane, THF, dioxane, acetonitrile, and toluene at the refluxing temperature of the respective solvents. Best yields were obtained when the reaction was performed in dichloroethane (DCE) at 80°C for 24 hours. Additives such as piperidine, acetic acid, and triphenylphosphine were added to the reaction mixture to examine the effect of base, acid, and nucleophiles on the reaction between **1** and **2**. We observed negligible to a detrimental role for these additives in controlling yield and product selectivity. In continuation, with an idea to develop a greener protocol [11], we attempted solvent-free reaction between **1** and **2**. Neat heating of a 1:1 mixture of **1** and **2** at 80°C for 5 hours did not lead to the formation of 1:1 adduct. However, at 110°C, product formation, albeit in low yield (32%), was observed after 1 hour. Prolonged heating at this temperature resulted in decomposition of both starting materials and product, and hence we abandoned solvent-free reaction as a viable alternative for preparing 1:1 adduct. Results obtained in screening experiments are collected in Table 1. Based on our findings, we selected refluxing a 1:1 mixture of **1** and **2** for 24 hours under nitrogen atmosphere in DCE at 80°C as the optimal condition for adduct formation. All subsequent reactions were performed under these optimized conditions.

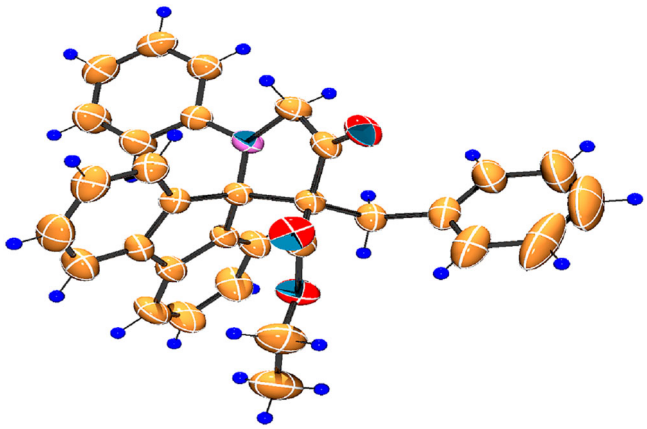
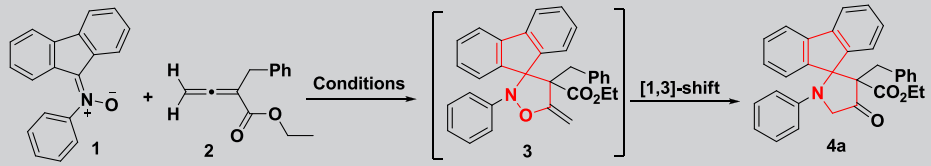


FIGURE 2 Single crystal XRD analysis of **4a** [Color figure can be viewed at wileyonlinelibrary.com]

The proposed mechanism for the formation of the spiro compound is depicted in Scheme 3. Based on earlier findings from our group [7] and several reports by Anderson [6], involvement of zwitterionic intermediate in the generation of formal cycloadduct **3** appears attractive. However, the absence of products arising through [3,3] shift is not consistent with the generation of a zwitterionic intermediate. Hence, we propose a typical cycloaddition reaction between **1** and **2** to yield the corresponding isoxazolidine **3** that undergoes further transformation to give **4**. Earlier reports on similar systems invoke N—O bond heterolysis as a key step in the isoxazolidine to pyrrolidinone rearrangement. It may be noted that N—O bond heterolysis can lead to two different products viz azepine derivative **10** and spiropyrrolidinone **4**. Since **10** was not formed in detectable amounts in our experiments, we rule out a mechanism involving N—O bond homolysis. An alternative pathway for the rearrangement of **3** to **4** involves a thermally allowed [1,3] shift—a process that is highly probable under the reaction conditions optimized for the generation of **4**. Based on these, we propose a domino sequence of two concerted processes ([1,3]-cycloaddition followed by [1,3] shift) as the most probable mechanism for the generation of **4**. To gain further support for the proposed mechanism, we attempted to isolate **3** with a view to establish its intermediacy. In pursuit of **3**, we stirred an equimolar mixture of **1** and **2** in DCE at room temperature for 4 days. GC-MS as well as TLC analysis of the reaction mixture indicated the presence of a new product identified as a 1:1 adduct based on GC-MS data. We attempted isolation of this product under carefully controlled conditions (flash chromatography followed by removal of solvent under subambient temperature). Even under these conditions, the product isolated was **4** indicating facile [1,3] shift in the initially formed **3** even under low-temperature conditions.

TABLE 1 Optimization of cycloaddition reaction conditions

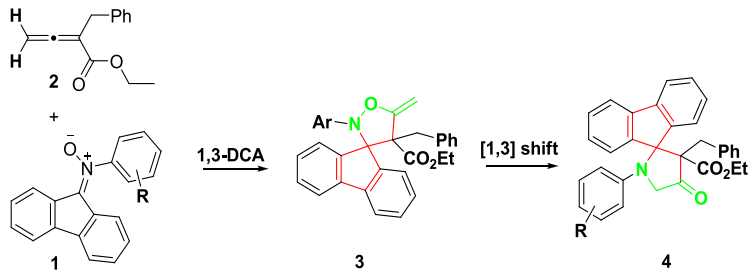


Solvent Temperature (°C) Additive **4a** Yield (%)

Solvent	Temperature, °C	Additive	4a Yield, %
DCM	RT		>5
DCM	40		>10
DCE	80		66
DCE	80	Acetic acid	30
DCE	80	Piperidine	28
DCE	80	Triphenyl phosphine	38
Acetic acid	100		-
Piperidine	100		-
MeCN	80		65
Toluene	110		64
THF	60		28
Cyclohexane	80		57
Dioxane	100		52
t-Butanol	80		58
p-Xylene	120		59
Ethanol	78		58
Solvent-free[a]	110		32

Reaction conditions: **1a** (1 mmol, 1 eq), **2** (1 mmol, 1 eq), 24 h, N_2 atmosphere.

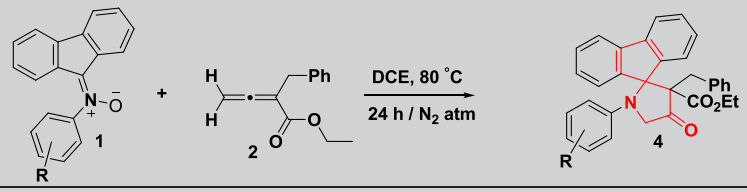
[a]Reaction time is 1 h.



SCHEME 3 Proposed mechanism for the formation of 4 from nitrone 1 and allene 2 [Color figure can be viewed at wileyonlinelibrary.com]

Several *N*-aryl nitrones were tested under optimized reaction conditions to determine the scope of the observed transformation. A 1,1-disubstituted allene such as **2** was employed in this investigation based on its higher stability under the reaction conditions employed by us and the ease of preparation and purification *vis* à *vis* the corresponding monosubstituted allenes. As shown in Table 2, in most cases, the reactions proceeded smoothly to afford the desired products in good yields. The reaction was compatible with several functional groups on the nitrone substrate including methoxy, methyl, and chloro in *ortho*, *meta*, and *para* positions. Nearly identical yields were obtained with **1a-j** indicating a negligible role for electronic factors in controlling reactivity. However the reaction of allene **2** with nitrones **1k, l** (**Chart 1**) with both *ortho* positions of *N*-aryl substituent blocked, the desired spiropyrrolidinone cycloadducts were not formed in detectable amounts even by GC-MS

TABLE 2 Scope of cycloaddition reaction



1	R	4	Yield, %
1a	H	4a	66
1b	4-Me	4b	63
1c	3-Me	4c	64
1d	2-Me	4d	61
1e	4-MeO	4e	60
1f	4-Cl	4f	61
1 g	3-MeO	4g	65
1 h	3-Cl	4h	68
1i	2-Cl	4i	62
1j	2-MeO	4j	60

Reaction conditions: **1** (1 mmol), **2a** (1 mmol), Solvent (8 mL), 24 h, N_2 atm.

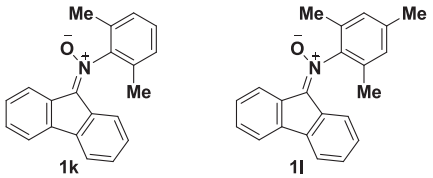


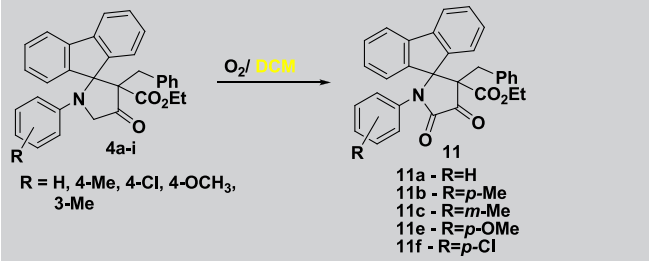
Chart 1

CHART 1 Fluorenyl nitrones with ortho and para positions blocked

and LC-MS; nitrones **1k,l** and allene **2** were recovered unchanged even after refluxing together in DCE for 4 days. This result clearly indicates the role of steric factors in inhibiting initial cycloaddition step.

During the course of our investigation, we observed that although **4a** is stable in the solid state, it undergoes slow decomposition in solution. In fact, our initial attempt to generate diffraction quality crystals of **4a** by slow evaporation of an ethanol solution resulted in quantitative transformation to a new product having 14 extra mass units. Careful analysis of spectral data of this material revealed its structure as **11** generated by aerial oxidation of **4a**. Consequently, we employed deaerated ethanol for subsequent recrystallizations. Interestingly, the nature of *N*-aryl substituents played a major role on facilitating aerial oxidation. Compounds having substituents at the *ortho* position and chloro and methoxy substituents at the *meta* position remained stable in solution. All other derivatives underwent efficient oxidation (Table 3). The effect of electronic and steric factors in controlling aerial oxidation step is currently under investigation.

TABLE 3 Oxidation of spiropyrrolidinones



Spiropyrrolidinone 4	Spiropyrrolidindione 11	Yield, %
4a	11a	48
4b	11b	50
4c	11c	51
4d	-	-
4e	11e	47
4f	11f	40
4g	-	-
4h	-	-
4i	-	-

2.1 | One-pot synthesis of diones 11

In an improved procedure for the synthesis of **11**, we refluxed an equimolar mixture of **1a** and **2** in DCE for

24 hours. The reaction mixture cooled to room temperature, saturated with air and stirred over silica gel (100 mg per mmol of **1a**) until TLC analysis indicated total disappearance of **4** [12]. From the reaction mixture, **11** could be isolated in yields comparable to those obtained in the two-step process. The reaction also affords product **11** in the absence of silica gel, but it took much more time (about 72 h).

3 | CONCLUSIONS

We have developed an efficient metal-free method for the synthesis of spiropyrrolidinones from *N*-aryl fluorenylnitrones and 1,1-disubstituted allenes. This reaction involves initial 1,3-dipolar cycloaddition followed by a [1,3] shift affording spiropyrrolidinones in good yields. Spiropyrrolidinones are stable in solid state, but in solution a few of them underwent aerial oxidation to give spiropyrrolidine-2,3-diones. These reactions are operationally simple and carried out under mild reaction conditions. Our method opens up a new approach toward the synthesis of spiropyrrolidinones that are found in many biologically active compounds and hence are important scaffolds in drug discovery.

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[#]Dedicated to Professor Richard D. McCullough on his sixtieth birthday.

ASSOCIATED CONTENT

[†]Supporting information for the paper including ^{1}H and ^{13}C NMR spectra of all the synthesized compounds and CIF of compound **4a** (CCDC No: 1889354) are available.

ORCID

U. Amrutha https://orcid.org/0000-0002-6008-8847
Sreedharan Prathapan https://orcid.org/0000-0002-8405-7818

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SUPPORTING INFORMATION

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