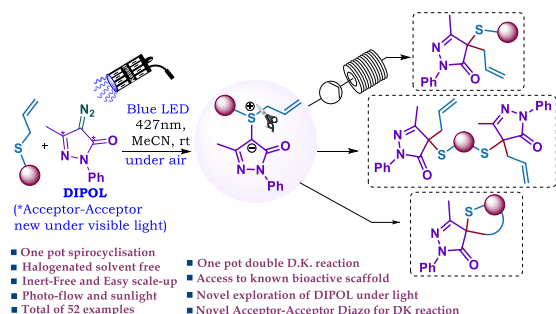# Reactivity of Acceptor-Acceptor Diazo-Pyrazolones with Allyl Thioethers under Visible Light: Access to Homoallyl and Bis-Homoallyl Sulfides, Spiropyrazolones- Pesticide Analogues and Photo-Flow Synthesis

Onkar S. Bankar,[a] Chhabi Pal,[a] Debasish Laha,[a] Abhijeet S. Sabale [a] and Ramakrishna G. Bhat*[a]

ABSTRACT: Pyrazolone framework has been greatly explored for various applications owing to their presence in many bioactive compounds. The novel reactivity of less selective and more reactive acceptor-acceptor kind of diazo pyrazolone (DIPOL) has been explored under visible light for the first time. We have successfully demonstrated the reaction of DIPOL and different allyl thioethers under blue light to construct a wide variety of products including pesticidal analogue exclusively in excellent chemo-selectivities in good to excellent yields. Moreover, the possible side products emanating from ketene were not observed. This protocol works smoothly in environmentally benign solvent under inert free condition. The practicality of the protocol has been extended to photo-flow reaction and also the reaction works smoothly under the direct exposure of sunlight.

The pyrazolone framework is a privileged structural motif and has been widely utilized in as dyes, bioactive and pharmaceutical compounds due to its versatility and applicability in diverse fields.[1,2] This interesting core scaffold is known to elicit anti-inflammatory, anti-tumor, neuroprotective, anti-bacterial, anti-fungal, and anti-pyretic properties and the newer pyrazalone derivatives have garnered a lot of interest in the pharmaceutical sector (Figure 1).[3] Spiropyrazolone derivatives are known to elicit anti-HIV properties and they are also proven type-4 phosphodiesterase inhibitors (Figure 1).[4]
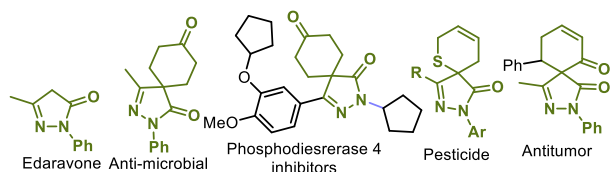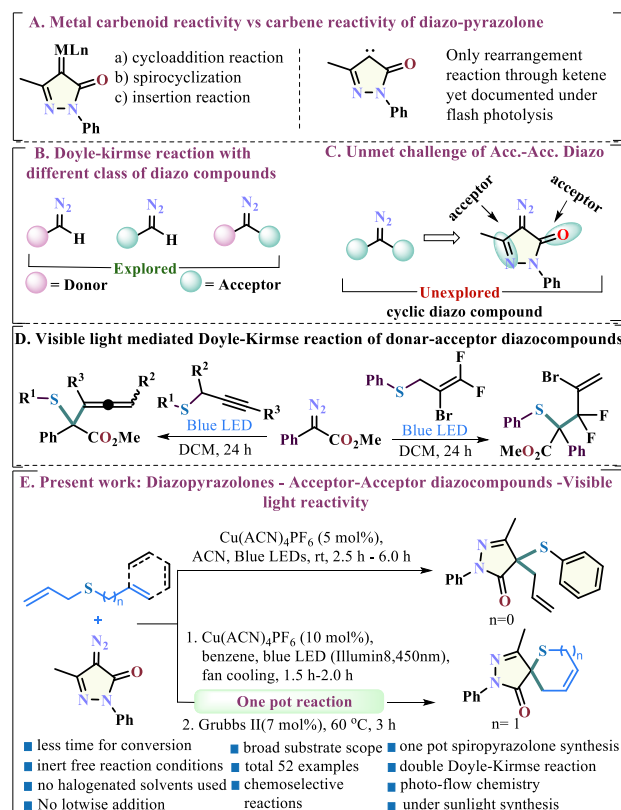

Figure 1. Functionalized Pyrazolone and Spiropyarazolone

Likewise, diazo compounds are also known for their versatile reactivity to access different useful scaffolds in organic synthesis.[5] In particular, the cyclic diazo compounds have received special attention as they are capable of showcasing intra-/inter molecular reactivity under different catalytic conditions. Cyclic diazo compounds have been explored for the C-H bond functionalization, cycloaddition, rearrangement reactions, etc.[6] Surprisingly, acceptor-acceptor cyclic diazo pyrazolone scaffold and its reactivity have been rarely explored using transition metal catalysis (Scheme 2A).[7] Moreover, the reactivity of diazo pyarazolones (DIPOL) under the irradiation of visible light or photolysis to generate carbene is unknown in the literature (Scheme 2A).[8]

The Doyle-Kirmse (D-K) reaction of diazo compounds and allylic sulfides under transition metal catalysis are known to furnish the products via [2,3]-sigmatropic rearrangement of allyl sulfonium ylides formed in situ. Generating the allyl sulfonium ylides efficiently via D-K reaction is very useful and has been explored to construct bioactive compounds and natural products.[9] The D-K reaction has been extensively studied on different types of donor,[10] acceptor,[11] and donor-acceptor[12] diazo compounds (Scheme 1B). However, to best of our knowledge, none of the acceptor-acceptor class of diazo compounds have been explored for the D-K reaction till date may be due to their reactivity (Scheme 1C).

Recently, Xiao and Gryko have independently reported the visible light mediated D-K reaction with allyl phenyl sulfide and propargyl phenyl sulfide to access the [2,3]-sigmatropic rearrangement D-K product (Scheme 1D).

Scheme 1. Carbene surrogates and their reactivity under visible light-Diazo Pyrazolones (DIPOL)

A. Metal carbenoid reactivity vs carbene reactivity of diazo-pyrazolone

B. Doyle-kirmse reaction with different class of diazo compounds

C. Unmet challenge of Acc.-Acc. Diazo

D. Visible light mediated Doyle-Kirmse reaction of donar-acceptor diazocompounds

E. Present work: Diazopyrazolones - Acceptor-Acceptor diazocompounds -Visible light reactivity

- less time for conversion
- inert free reaction conditions
- no halogenated solvents used
- No lotwise addition
- broad substrate scope
- total 52 examples
- chemoselective reactions
- one pot spiropyrazolone synthesis
- double Doyle-Kirmse reaction
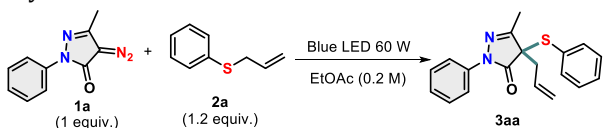- photo-flow chemistry
- under sunlight synthesis

However, these interesting and elegant protocols rely on halogenated solvent, inert atmosphere, super stoichiometric amount of allyl thioethers and requires a lot-wise addition of acceptor-donor diazo compound (Less reactive and more stable diazo compound).

Inspired by previous reports and owing to the importance of pyrazolones, we hypothesized that acceptor-acceptor diazo compounds such as DIPOLs could undergo dinitrogen extrusion under suitable visible light to form carbene intermediate in situ so as to explore the D-K reaction with various allyl thioethers to access biologically relevant pyrazolone derivatives.

In order to validate our hypothesis, we commenced with model reaction of diazo edaravone (DEDA) **1a** and allylic phenyl sulfide **2a** in EtOAc under the irradiation of blue LED light (60 W). Gratifyingly the reaction afforded the desired product **3aa** in modest yield (26%, Table 1, Entry 1). Interestingly, we did not observe any rearrangement products emanating through ketene. Encouraged by the initial result, we carried out the further optimization by screening different solvents (see ESI, *Table S1, page 11*) and among all MeCN proved to be most advantageous to afford the desired product **3aa** in moderate yield (60%, Table 1, Entry 2). Halogenated solvents (DCM, CHCl₃) and polar aprotic solvents with nucleophilic sites such as THF or 1,4-dioxane proved to be not compatible (see ESI, Table S1). The reaction in polar protic solvents (H₂O, MeOH, EtOH) worked very sluggishly to afford the desired product in poor yields (up to 14%, 30 h, See ESI *Table S1*). Later we screened different light sources of specific wavelength and among all 427 nm - blue LEDs proved to be the best for the efficient

transformation to obtain the desired product **3aa** in higher yield in lesser time at rt (Table 1, Entry 3).

Table 1. Optimization Studies of the Visible Light-mediated Doyle-Kirmse reaction.[a]
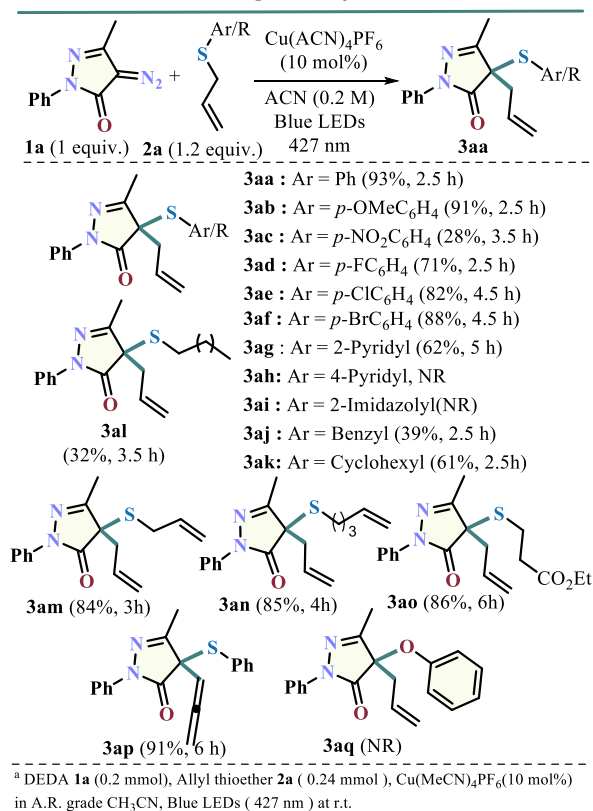

Entry	Deviations from tested conditions[a]	Yield[b] (%) of **3aa**
1	None	28(26)
2[d]	MeCN	60
3[d]	427 nm blue LED,	68
4[d]	No Light, 78 °C	NR
5[d]	427 nm, AgSbF₆	86
6[d]	**427 nm, Cu(ACN)₄PF₆**	**93(91)**
7[d]	No light, Cu(ACN)₄PF₆, 78 °C	NR

[a]**Reaction conditions**: DIPOL **1a** (0.2 mmol, 1.0 equiv.), allyl phenyl sulfide **2a** (0.24 mmol, 1.2 equiv.), MeCN (c = 0.1 M), irradiated with blue LEDs (60 W) at room temperature (27 °C), 16 h. [b]Yields of **3aa** were determined by ¹H NMR spectroscopic analysis of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]Iso-lated yield of the products was given in the parentheses. [d] A. R. grade CH₃CN was used. NR = No reaction

The reaction in the absence of light (at room temperature as well at an elevated temperature 78 °C) did not afford the desired product **3aa** (Table 1, Entry 4).

Scheme 2. Substrate scope of Allyl thioethers[a]

3aa : Ar = Ph (93%, 2.5 h)
3ab : Ar = p-OMeC₆H₄ (91%, 2.5 h)
3ac : Ar = p-NO₂C₆H₄ (28%, 3.5 h)
3ad : Ar = p-FC₆H₄ (71%, 2.5 h)
3ae : Ar = p-ClC₆H₄ (82%, 4.5 h)
3af : Ar = p-BrC₆H₄ (88%, 4.5 h)
3ag : Ar = 2-Pyridyl (62%, 5 h)
3ah: Ar = 4-Pyridyl, NR
3ai : Ar = 2-Imidazolyl(NR)
3aj : Ar = Benzyl (39%, 2.5 h)
3ak: Ar = Cyclohexyl (61%, 2.5h)

3al (32%, 3.5 h)

3am (84%, 3h) **3an** (85%, 4h) **3ao** (86%, 6h)

3ap (91%, 6 h) **3aq** (NR)

[a] DEDA **1a** (0.2 mmol), Allyl thioether **2a** (0.24 mmol), Cu(MeCN)₄PF₆(10 mol%) in A.R. grade CH₃CN, Blue LEDs (427 nm) at r.t.
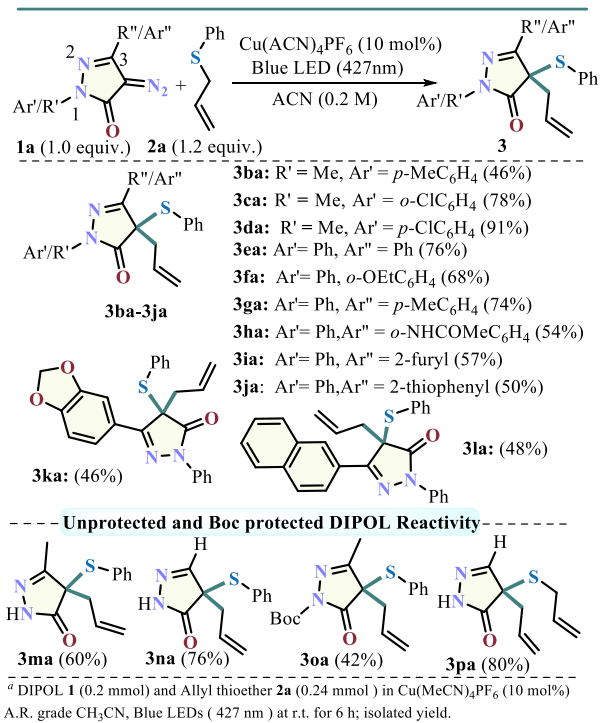
This result unambiguously proved that light is an essential energy source for the key transformation. We further screened various additives in order to explore the possibility of enhancing the yield of desired product **3aa** (see ESI *Table S3 page 13*). Surprisingly, among all the

additives, silver and copper salts enhanced the yield of **3aa** significantly (Table 1, Entries 5, 6). To confirm the exact role of copper complex whether it acts as an additive or as a catalyst (which may form copper-carbenoid with **1a**), we performed the reaction of **1a** and **2a** in presence of Cu(ACN)$_4$PF$_6$ from rt to 78 °C (absence of light) in MeCN (Table 1, Entry 7). However, the reaction did not afford **3aa** thus ruling out the formation of copper-carbenoid if any (thermal process). Based on the exhaustive screening, **1a** (1 equiv.), allylic phenyl sulfide **2a** (1.2 equiv.), Cu(ACN)$_4$PF$_6$ (10 mol%) in MeCN under Blue LEDs (427 nm) at room temperature proved to be the optimum condition to access **3aa** (Table 1, Entry 6).

Having optimized the reaction condition, so as to generalize the protocol, we explored the diverse substrate scope of allyl thioether (Scheme 2). In this regard, we synthesized a variety of thioethers **2b-2q** having saturated, unsaturated, cyclic and acyclic groups. Initially, we focused on *para*-substituted-aryl sulfides and upon treatment with DEDA **1a** under the optimized reaction conditions successfully furnished the corresponding rearrangement products **3ab–3af** (up to 91%, Scheme 2).

Scheme 3. Substrate scope of Diazopyrazolone[a]

3ba: R' = Me, Ar' = *p*-MeC$_6$H$_4$ (46%)
3ca: R' = Me, Ar' = *o*-ClC$_6$H$_4$ (78%)
3da: R' = Me, Ar' = *p*-ClC$_6$H$_4$ (91%)
3ea: Ar'= Ph, Ar'' = Ph (76%)
3fa: Ar'= Ph, *o*-OEtC$_6$H$_4$ (68%)
3ga: Ar'= Ph, Ar'' = *p*-MeC$_6$H$_4$ (74%)
3ha: Ar'= Ph, Ar''= *o*-NHCOMeC$_6$H$_4$ (54%)
3ia: Ar'= Ph, Ar'' = 2-furyl (57%)
3ja: Ar'= Ph, Ar''= 2-thiophenyl (50%)

3ka: (46%)   **3la:** (48%)

– – – – Unprotected and Boc protected DIPOL Reactivity – – – – – – –

3ma (60%)   **3na** (76%)   **3oa** (42%)   **3pa** (80%)

[a] DIPOL **1** (0.2 mmol) and Allyl thioether **2a** (0.24 mmol) in Cu(MeCN)$_4$PF$_6$ (10 mol%) A.R. grade CH$_3$CN, Blue LEDs (427 nm) at r.t. for 6 h; isolated yield.
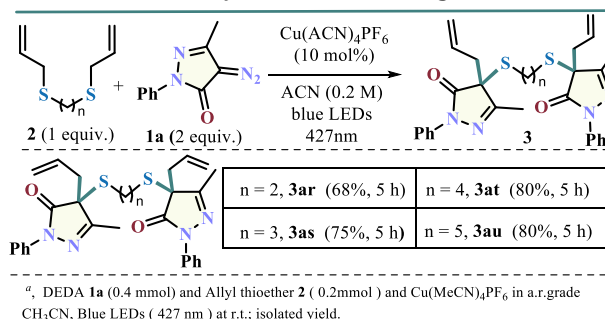
It's observed that the electron donating as well as electron withdrawing substituents on allyl phenyl sulfide furnishes corresponding products **3ab** (91%), **3ac** (28%) in excellent and modest yield respectively. This may be due to the influence of electronic factor on the varied nucleophilicity of the sulfur atom. The allyl sulfide having deactivating groups (F, Cl and Br) also worked well to afford the desired products (**3ad-3af**) (up to 88%). The heteroaromatic, benzylic and cyclohexyl, long chain alkyl derived all sulfides afforded the desired products (**3ag, 3aj, 3ak, 3al**) while the 4-pyridyl (**2h**) and 2-imidazolyl (**2i**) derived allyl sulfides did not react (Scheme 2). Allyl thioether containing terminal alkenes (**2m-2o**) also worked smoothly to furnish the corresponding products **3am-3ao** in very good yields (up to

85%). We did not observe any side products due to the cyclopropanation with DEDA. The phenyl propargyl thioether (**2p**) worked well to give the corresponding **3ap** in excellent yield (up to 91%). However, allyl phenyl ether **2q** under optimized condition did not react (Scheme 2).
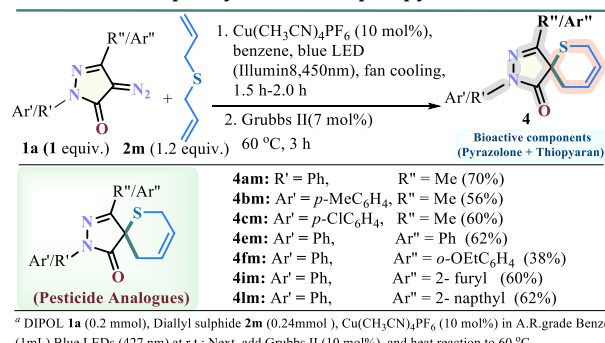
Later, we synthesized a variety of diazo pyrazolones (**1a-1r**) and explored their reactivity. Substrates containing substituents on *N*1 of DIPOL upon treatment with allyl phenyl sulfide **2a** afforded the corresponding desired products **3ba-3da** in moderate to excellent yields (Scheme 3). Variation in the outcome of yields is attributed ability to stabilize the negative charge of the ylide species during the course of reaction. Aryl, heteroaryl substituents on C3 of *N*-phenyl diazo edaravone reacted smoothly with allyl phenyl sulfide **2a** to afford the corresponding desired products **3ea-3la** in moderate to good yields (up to 74%, Scheme 3). Gratifyingly, bulky naphthyl derivative as well dioxalane derived substrates well tolerated the reaction conditions (**3ka, 3la**). More importantly, unprotected as well as protected pyrazolone derivatives reacted smoothly with **2a** to afford corresponding products (**3ma-3pa**) in good to very good yields (up to 80%, Scheme 3). It's important to highlight that many bioactive scaffolds need free NH group for hydrogen bonding for eliciting the bioactivity and the protocol effectively avoided protection-deprotection as a proof of concept.

Scheme 4. Double Doyle-Kirmse Rearrangement[a]

| n = 2, **3ar** (68%, 5 h) | n = 4, **3at** (80%, 5 h) |
| n = 3, **3as** (75%, 5 h) | n = 5, **3au** (80%, 5 h) |

[a], DEDA **1a** (0.4 mmol) and Allyl thioether **2** (0.2mmol) and Cu(MeCN)$_4$PF$_6$ in a.r.grade CH$_3$CN, Blue LEDs (427 nm) at r.t.; isolated yield.

Encouraged by the initial success of D-K reaction on novel pyrazolone scaffold, we planned to synthesize a range of intriguing molecules by executing the double D-K reaction by strategically utilizing the long chain diallyl di-sulfides. In this regard, we synthesized various long-chain diallyl disulfides (**2r-2u**). Gratifyingly, the reaction of DEDA (2 equiv.) with different diallyl disulfides (**2r-2u**) afforded the corresponding desired products (**3ar-3au**) in good to very good yields at rt (up to 80%) under standard conditions (Scheme 4).
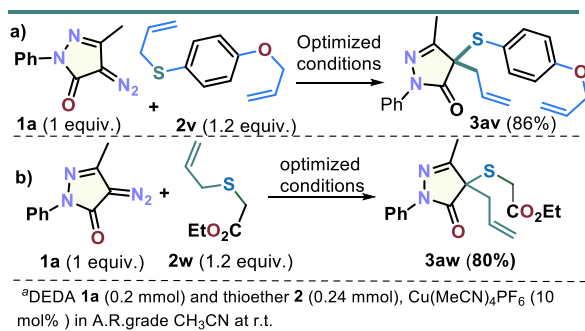
Scheme 5. One pot synthesis of spiropyrazolone

4am: R' = Ph, R'' = Me (70%)
4bm: Ar' = *p*-MeC$_6$H$_4$, R'' = Me (56%)
4cm: Ar' = *p*-ClC$_6$H$_4$, R'' = Me (60%)
4em: Ar' = Ph, Ar'' = Ph (62%)
4fm: Ar' = Ph, Ar'' = *o*-OEtC$_6$H$_4$ (38%)
4im: Ar' = Ph, Ar'' = 2- furyl (60%)
4lm: Ar' = Ph, Ar'' = 2- napthyl (62%)

[a] DIPOL **1a** (0.2 mmol), Diallyl sulphide **2m** (0.24mmol), Cu(CH$_3$CN)$_4$PF$_6$ (10 mol%) in A.R.grade Benzene (1mL),Blue LEDs (427 nm) at r.t.; Next, add Grubbs II (10 mol%) and heat reaction to 60 °C.

Pyrazolone as well as thiopyran derivatives are known for their potent bioactivities.[3] Also, interestingly, pyrazolone fused thiopyrans (spiropyrazolone - shown in Figure 1, Scheme 5) are known as potent pesticides.[4] Encouraged by the success obtained through this protocol, we further planned to synthesize a few spiropyrazolones in one pot under visible light conditions. Gratifyingly, the model substrates **1a** and **2m** under the reaction conditions afforded the desired product **3am** in good yield (84%). Later, **3am** under Grubbs metathesis conditions afforded the desired spiropyrazolone **4am** in 85% yield (See ESI, Page S7).

Inspired by this success, we planned to execute this reaction in one-pot using a parallel synthesizer Illumin8 (450 nm blue LEDs).[13] In this regard, different DIPOLs (**1a-1c, 1e, 1f, 1i, 1l**), diallyl sulfide **2m**, Copper catalyst (10 mol%) were loaded in 7 different reaction vessels of a Illumin8 and were irradiated by Blue LED (450 nm, 1.5 - 2 h, monitored by TLC). After which, the Grubbs II catalyst (10 mol%) was added to the crude reaction mixture and stirred for 3 h at an elevated temperature without irradiation of light. Gratifyingly, we obtained the corresponding spiropyrazolone products by achieving the D-K reaction and ring closing metathesis in one-pot (**4am-4cm, 4em, 4fm, 4im, 4lm**) in moderate to good yields (Scheme 5).

Scheme 6. Chemoselectivity – D-K vs Stevens Reaction

a)

b)

*a*DEDA **1a** (0.2 mmol) and thioether **2** (0.24 mmol), Cu(MeCN)$_4$PF$_6$ (10 mol%) in A.R.grade CH$_3$CN at r.t.

In order to examine the chemoselectivity of this transformation, we synthesized the substrate **2v** (having both *O*-ally thio- and *S*-allyl ether moieties) that has two potential sites to form either sulfur ylide or oxygen ylide. Interestingly, the reaction of **2v** with DEDA **1a** under the optimized reaction condition furnished the corresponding **3av** exclusively as a sole product (86% yield, Scheme 6a). This clearly indicated that sulfur ylide is more favourable and preferred over oxygen ylide possibly due to the higher electronegativity of the oxygen atom that makes the oxygen ylide relatively less stable. Later we synthesized compound **2w** in order to examine the competitive reaction between Doyle-Kirmse and [2,3] stevens reaction. The reaction of **1a** and **2w** exclusively favoured the D-K reaction over [2,3] sigmatropic reaction to furnish desired product **3aw** in higher yield (80% yield, Scheme 6b).

After successfully exploring the novel synthetic protocol for achieving the D-K reaction on newer diazo scaffold, we became intrigued in studying blue-light-induced carbene formation under continuous-flow conditions for the further application. Flow chemistry is particularly well-suited for performing photochemical transformations due the small channel diameters and large reaction surface area enhance the penetration of photons into the reaction

solution. In this regard, we carefully examined the photo-flow reaction of the protocol in gram quantity. Unlike the traditional batch process (an average reaction time of 4.5 h), the coil reactor enabled quantitative conversion of DEDA **1a** (same light source as in Batch Process, 427 nm) to afford the corresponding desired product **3am** in excellent yield in a shorter reaction time (2 h, 90%, Scheme 7a, See ESI for details).

Scheme 7. Applications: Photo-Flow and Sun-light reactions
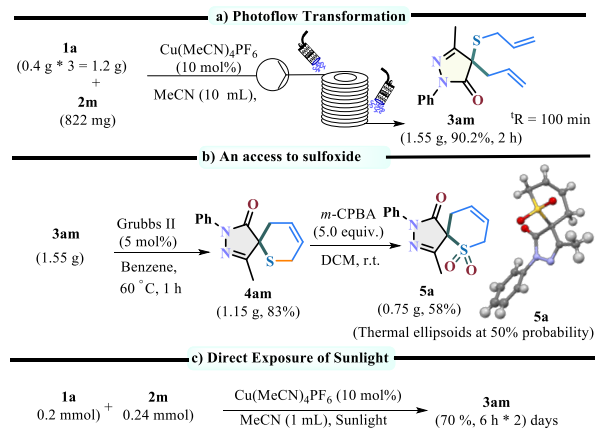
This result clearly highlights the potential of continuous flow processes for the reaction intensification. This application provides an access to reaction parameters that are not attainable in conventional batch chemistry. Further in order to explore the late-stage application of this protocol **3am** (1.55 g) was subjected to the ring closing metathesis to obtain the compound **4am** in excellent yield (Scheme 7b). This upon treatment with *m*-CPBA afforded the corresponding sulfoxidation product **5a** in **58%** yield (Scheme 7b). Later, we explored the reaction of **1a** and **2m** under the direct exposure of sunlight while maintaining other optimized reaction conditions (Scheme 7c). Gratifyingly, we obtained the desired product **3am** in good yield (70%).

Scheme 8. Plausible Mechanism of the transformation
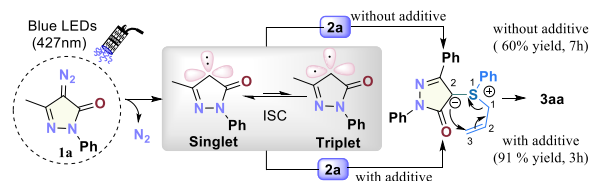
In order to have some insights into the reaction pathway we performed a series of control experiment and the plausible mechanism is proposed (Scheme 8). We have also carried out the UV-Visible studies, HLPC studies to understand the role of copper salt as a catalyst or additive and radical trapping experiment to study the nature of the reaction pathway (See ESI for details). Based on the observation and available literature precedence, we propose **1a** undergoes photolysis to generate the singlet carbene which further reacts **2a** to afford the **3aa** via [2,3] sigmatropic rearrangement and the copper salt may act as an additive not as a catalyst.

In summary, we have successfully demonstrated novel reactivity of acceptor–acceptor diazo compound such as DIPOL under visible light irradiation to achieve Doyle-Kirmse reaction. The bench-stable diazo pyrazolones have been effectively employed for the double Doyle-Kirmse reaction to access bis-allyl sulfides, spiropyrazolones under visible light. The established protocol demonstrated a wide substrate scope and good functional group tolerance. The application of the protocol was further demonstrated on continuous-flow setup and the reaction also works under the direct exposure of sun-light. The method gives an access to construct the bioactive pyrazolone fused thiopyran scaffold and pesticide analogue framework. The protocol is also proved to be scalable.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the Publications website. The reaction optimization tables, procedure for reaction, series of control experiments, Photo-flow synthesis and Sun-light Synthesis procedure, characterization data for all new compounds and copies of ^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra (PDF).

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13 The one pot reaction reaction at room temperature was too sluggish and worked well at an elevated temperature (60 ºC) in benzene as acetonitrile is not proved to be good in case of Grubbs metathesis. In this regard, Parallel Reactor-Illumin8 was used with available LED cartridges (450 nm) and hence it might have led to desired products relatively in lower yields in comparison to 427 nm.