Progress Report

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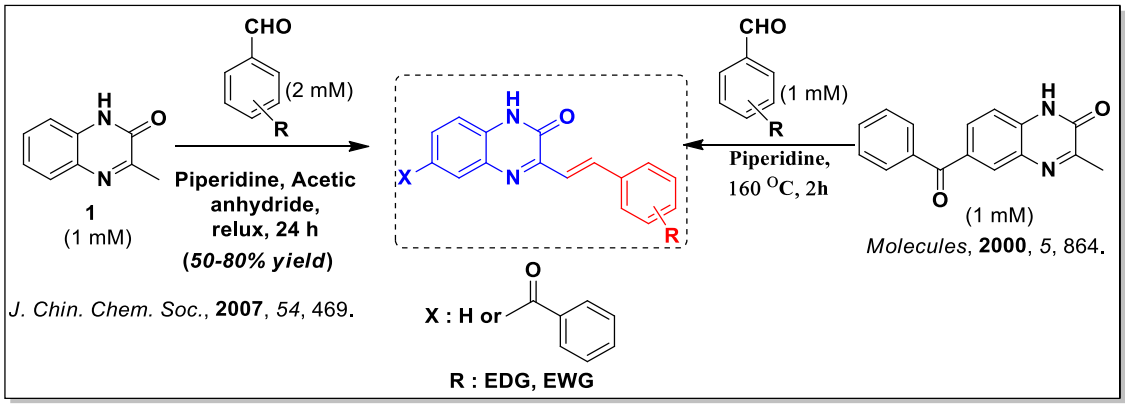
Design, synthesis of styrylquinoxalinones and their rigidified analogs as Anti-alzheimer agents

Styrylquinoxalin-2(1*H*)-ones are the hybrid molecules of styryl and quinoxalinone which display various pharmacological properties such as anticancer agents,[1] glucagon receptor antagonist[2] antiangiogenic effect (VEGFR-2 inhibition)[3] etc. Owing to this, Refaat and co-workers reported the synthesis of styrylquinoxalin-2(1*H*)-ones by condensing 3-methylquinoxaline-2-(1*H*)-one with aldehydes using acetic anhydride as solvent in presence of piperidine in 24h.[4] However, Ammar *et. al* reported the fusion reaction of 3-methylquinoxaline-2-(1*H*)-one derivatives with aldehydes in presence of piperidine in 2h (**Scheme 1**).[5]



Scheme 1 : Literature reports for the synthesis of Styrylquinoxalin-2(1*H*)-ones

[1] (d) M. N. Noolvi, H. M. Patel, V. Bhardwaj and A. Chauhan, Eur. J. Med. Chem., 2011, 46, 2327–2346; (e) H. A. Abbas, A. R. Al-Marhabi, S. I. Eissa and; Y. A. Ammar, Bioorg. Med. Chem., 2015, 23, 6560–6572; (f) Z. Liu, S. Yu, D. Chen, G. Shen, Y. Wang, L. Hou, D. Lin, J. Zhang and F. Ye, Drug Des., Dev. Ther., 2016, 10, 1489– 1500;

[2]) M. Negwer and H. G. Scharnow, in Organic chemical drugs and their synonyms, Wiley, Weinheim, 2001, vol. 2–3, 869;

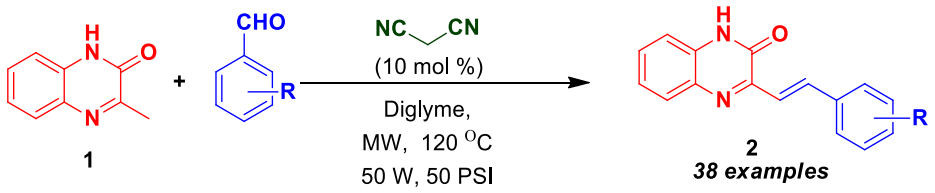
[3] L. Shi, J. Zhou, J. Wu, J. Cao, Y. Shen, H. Zhou and X. Li, Bioorg. Med. Chem., 2016, 24(8), 1840–1852;

[4] M. M. Badran, A. A. Moneer, H. M. Refaat, A. A. El-Malah, *J. Chin. Chem. Soc.* **2007**, *54*, 469.

[5] M. M. Ali, M. M. Ismail, M. S. El-Gaby, M. A. Zahran, Y. A. Ammar, *Molecules* **2000**, *5*, 864

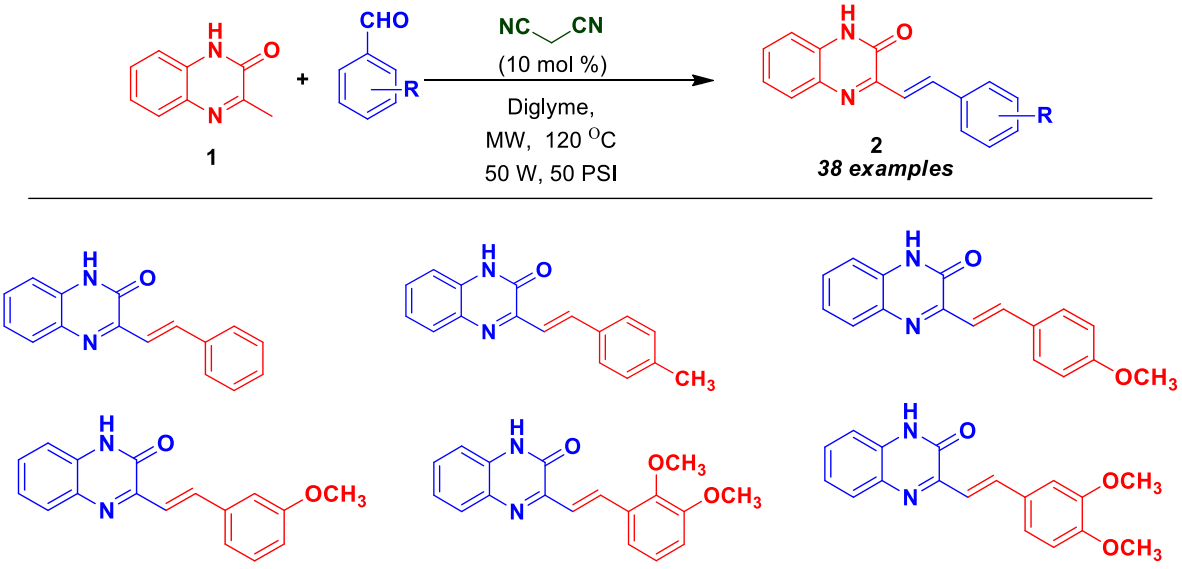
However the literature reports are not greener from the view of energy and use of hazardous reagents. Thus, we find alternative approaches to access styrylquinoxalin-2(1*H*)-ones **2** by employing (i) malanonitrile as activating handle,[6] (ii) $FeCl_3$,[7] and (iii) Ba/PANI as catalyst.[8]

(i) In 2021, we have devised a new acid/base-free simple and efficient malononitrile-activated condensation of 3-methylquinoxalinone **1** with aryl aldehydes for synthesis of styrylquinoxalin-2(1*H*)-ones **2** in excellent yields (**Scheme 2**).

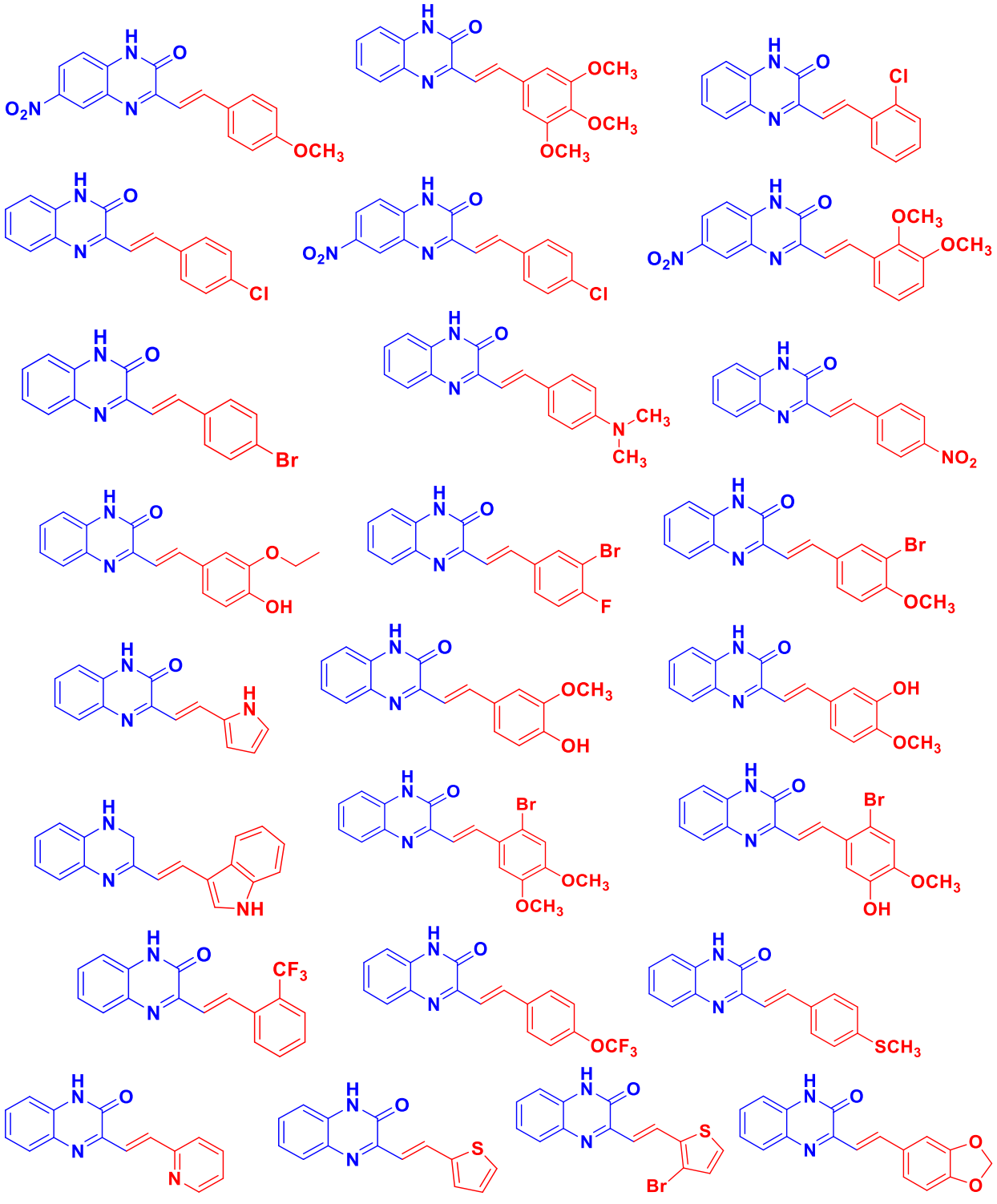


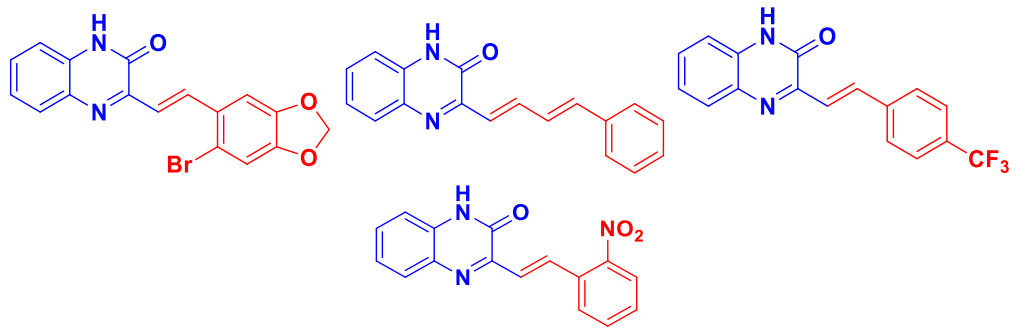
Scheme 2: Synthesis of *(E)*-3-(4-methoxystyryl)quinoxalin-2(1*H*)-one using malanonitrile as an activating handle.

Subsequently, using this methodology, a diverse range of styrylquinoxalin-2(1*H*)-ones were synthesized, as summarized in **Scheme 3**.



[6] S. Mahajan, N, Slathia, K. K. Kapoor, ***RSC Adv.***,2020, **10**, 15966-15975.
[7] R. P. Sharma, S. Mahajan, N. Slathia and K. K. Kapoor, *Synth. Commun.*, **2021**, https://doi.org/10.1080/00397911.2022.2070435.
[8] L. Devi, A. Gupta, *Polycycl Aromat Compd*.,**2022**, https://doi.org/10.1080/10406638.2022.2039235.





Scheme 3: Substrate scope for synthesis of 3-substituted styrylquinoxalin-2(1*H*)-ones **2** from 3-methylquinoxalinones **1** and aryl/hetaryl aldehydes.

Additionally, the computational design and the biological evaluation of the series of prepared compounds were carried out. The computational studies on the donepezil-bound crystal structure of human acetylcholinesterase (4EY7) revealed that "styrylquinoxalin-2(1*H*)-one" scaffold perfectly occupies the active site gorge of the enzyme; and display all key interactions required to inhibit the catalytic activity of the enzyme **(Figure 1)**. Also, **Figure 2** reveals molecular docking of styrylquinoxalin-2(1*H*)-ones with human AChE (PDB: 4EY7). It was found that the synthesised compounds exhibit weak to moderate activity against cholinesterase enzymes, thus, opening up a new chemotype for dual inhibition of these enzymes.

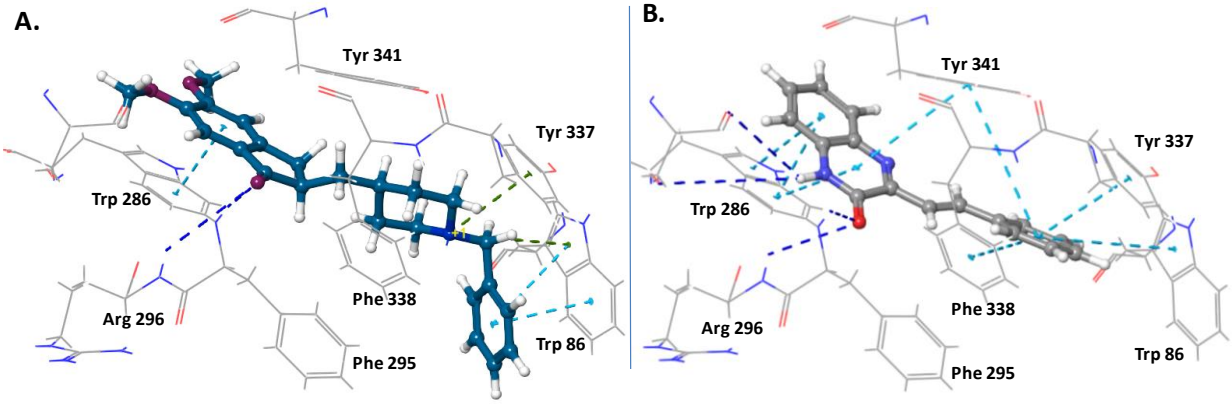


Fig 1. Styrylquinoxalin-2(1*H*)-ones as AChE inhibitors. **A**. Interactions of donepezil with AChE; **B**. Interactions of styrylquinoxalin-2(1*H*)-one scaffold with AChE catalytic site gorge.

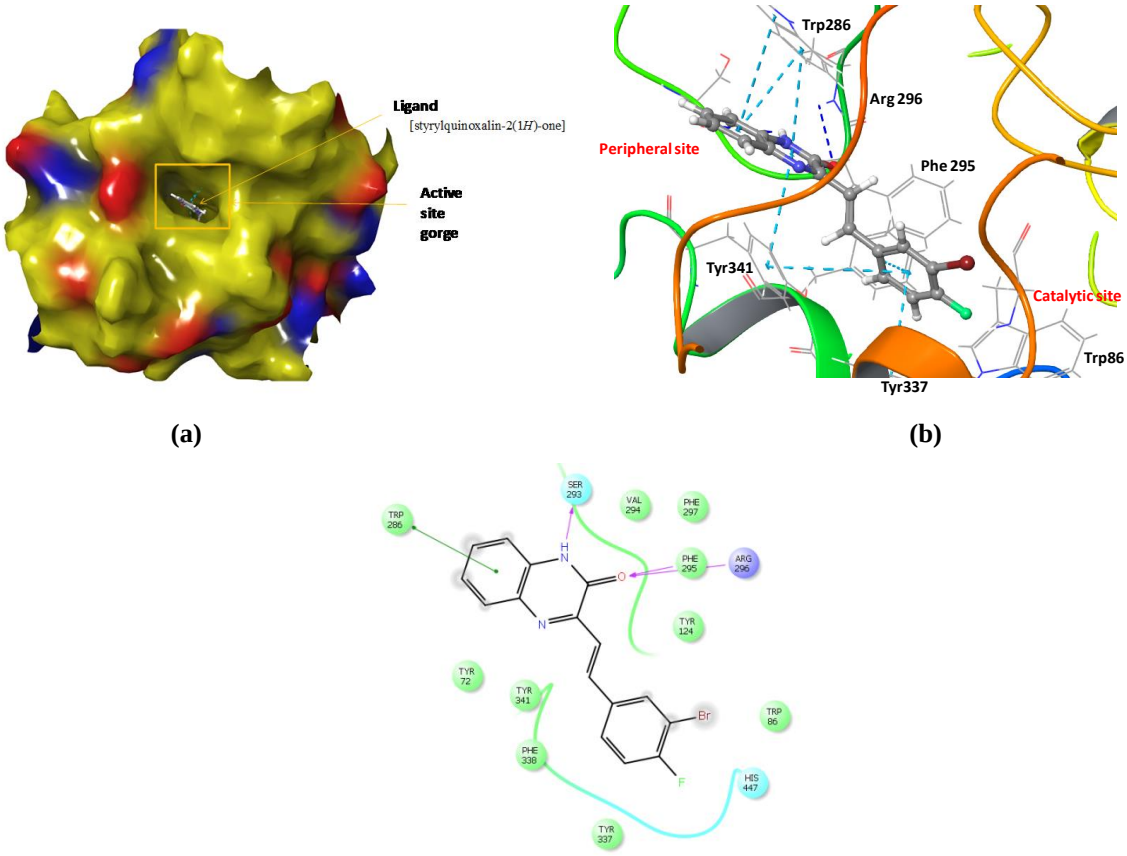
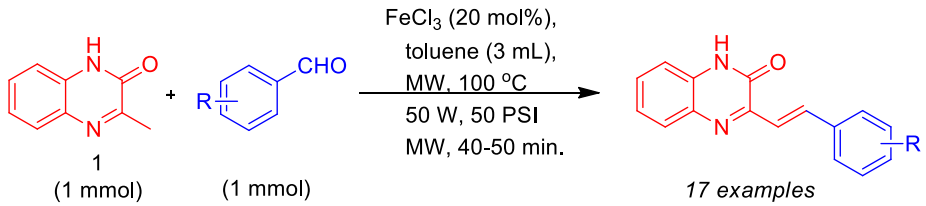


Fig 2 : (a) Surface view, (b) 3D-view, (c) 2D-view

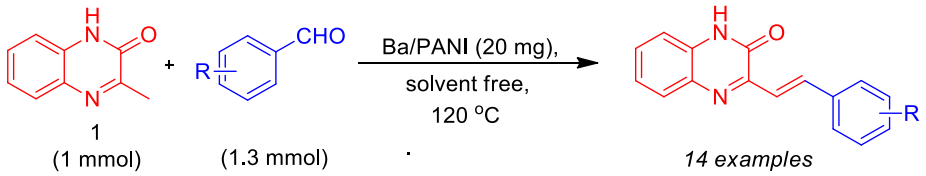
(ii) In another approach, we utilized $FeCl_3$ as a catalyst to provide a new and efficient entry to styrylquinoxalin-2(*1H*)-ones **2**. In literature, this is the first report to explore a metal catalyst as Lewis acid for the synthesis of styrylquinoxalin-2(1*H*)-ones **2** from 3-methylquinoxalin-2(1*H*)-one **1** and aryl aldehydes (**Scheme 4**).



Scheme 4: $FeCl_3$ catalysed synthesis of 3-substituted styrylquinoxalin-2(1*H*)-ones.

The highlights of the methodology to access (*E*)-3- substituted styrylquinoxalin-2(1*H*)-ones **2** is use of less toxic, environmentally benign, and easily available $FeCl_3$ as catalyst. The foremost aspect of the protocol is milder reaction conditions, higher yields, ease of work up, lesser reaction time, and mild nature of catalyst.

(iii) In contrast, Barium chloride embedded polyaniline (Ba/PANI) nanocomposite has been utilized as a heterogeneous nanaocatalyst to afford bioactive scaffold styrylquinoxalin-2(1*H*)-ones **2** in excellent yields (**Scheme 5**). This is the first report in literature to employ Ba/PANI as a nanocatalyst in organic synthesis.

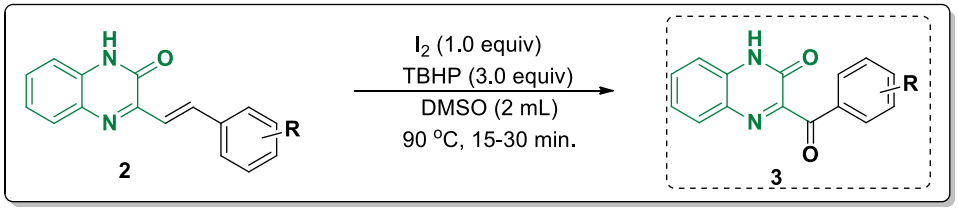


Scheme 5: Ba/PANI catalysed synthesis of 3-substituted styrylquinoxalin-2(1*H*)-ones.

The results showed that Ba/PANI nanocatalyst offered notably higher catalytic activity compared to both $BaCl_2$ and PANI and was easily recoverable and reusable. The synthesized barium containing nanocomposite has been characterized by XRD, FTIR, SEM, HR-TEM, EDX, ICP-MS, UV–Vis, TGA, N_2 adsorption–desorption isotherms (BET), and XPS techniques.

Thus, a broad spectrum of styrylquinoxalinones were prepared by employing malanonitrile or $FeCl_3$ or Ba/PANI. Consequently the synthesized compounds were further discovered as starting material to develop a series of benzoylquinoxalinones. Iodine/TBHP mediated a facile metal-free oxidative rearrangement of 3-styrylquinoxalin-2(1*H*)-one **2** in DMSO *via* Kornblum oxidation was explored for the synthesis of 3-aroylquinoxalin-2(*1H*)-ones **3** in good to high yields (**Scheme 6**).[9]

[9] N. Slathia, A. Gupta, K. K. Kapoor, *Tetrahedron. Lett.*, **2021**, *78*, 153268.



Scheme 6: Synthesis of 3-aroylquinoxalin-2(*1H*)-ones from 3-styrylquinoxalin-2(1*H*)-ones.

The methodology proceeds under mild conditions *via* oxidative aryl migration, followed by C−C bond cleavage *via* intramolecular oxidative rearrangement. The protocol is rapid with single step, simple, economical, and better yielding.

OVERALL: Three publications in journals of international repute

Based on the valuable inputs in the relative areas of chemistry two projects have been submitted for funding:

I. **SERB, DST**
II. **JKSTIC**