PHOTOINDUCED SYNTHESIS OF 4*H*-BENZO[*E*]PYRAZOLO[1,5-B][1,2,4]THIADIAZINE DERIVATIVES BY INTRAMOLECULAR C-N COUPLING

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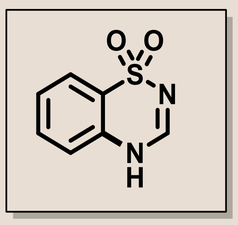
1 Introduction.

Sulfonamides represent an important family of compounds with diverse biological activities, especially recognized as antibiotics. 1,2,4-Benzothiadicines-1,1-dioxide belong to a family of cyclic sulfonamides with significant pharmacological applications, such as antimicrobial, antiviral and antidiabetic. In addition, they are used clinically as diuretics and antihypertensives.[1]

Scientific research has focused mainly on substituted 1,2,4-benzothiadicines, but not so much on fused systems such as azolo[1,2,4]benzothiadiazine. However, triazolo[1,2,4]benzothiadiazine derivatives have been shown to have potent antiproliferative and antibacterial activities, which has sparked great scientific interest in the development of new synthetic routes for cyclic sulfonamides. Existing synthesis routes typically involve the use of metals, high temperatures and long reaction times, making them expensive and environmentally damaging. Therefore, there is interest in developing more innovative and sustainable synthetic strategies.

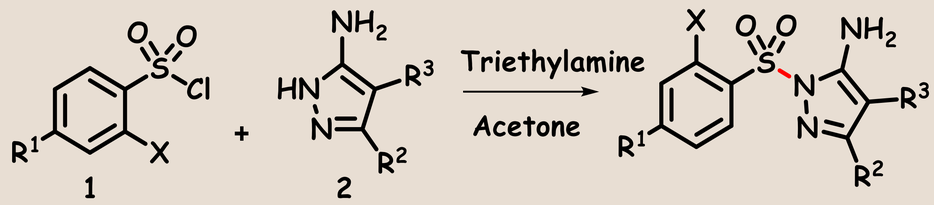
2 General objective.

To design a synthetic route of 4*H*-benzo[*e*]pyrazolo[5,1c][1,2,4]thiadiazines through intramolecular arylation reactions free of transition metals, ligands and at room temperature.



4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide.

3 Synthesis of precursors.



X= Cl, Br

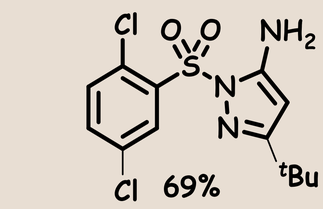
R1= F, CF_3, Me, Cl, OCF_3

R2= H, Me, Ph

R3= H, Et

Reaction conditions: 2-halo-benzenesulfonyl chloride (**1**, 1 eq.), amino pyrazole (**2**, 1 eq.), ET3N (1 eq.), acetone (5 mL), 25 °C, 8 hours.

4 Preparation of 1-((2-halophenyl)sulfonyl)-1H-pyrazol-5-amines.



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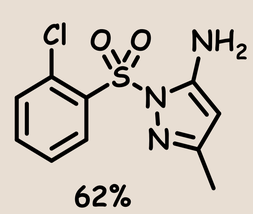

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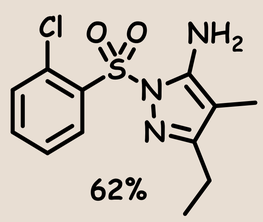

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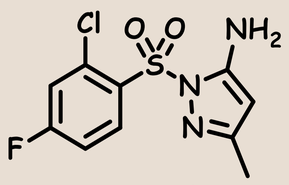

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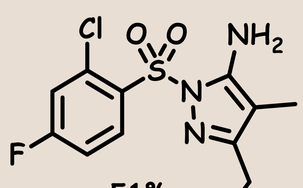

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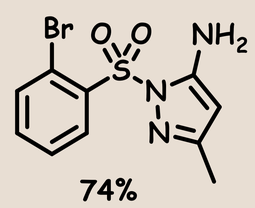

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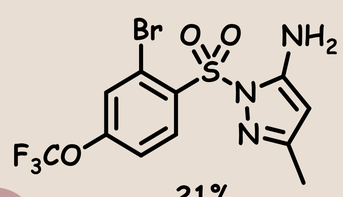

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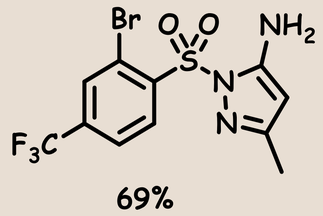

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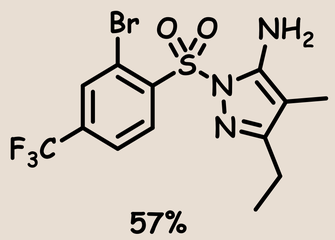

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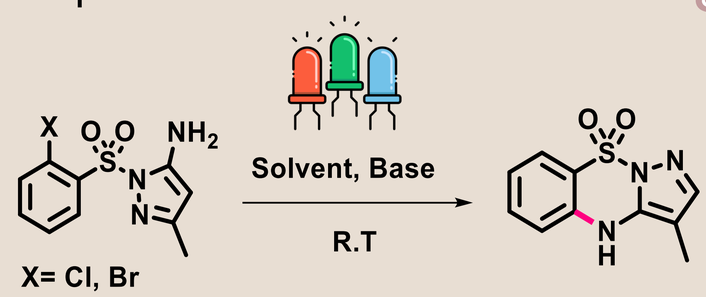
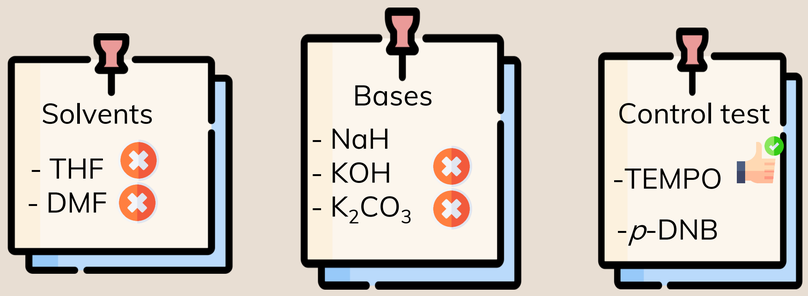
5 Optimization of conditions.

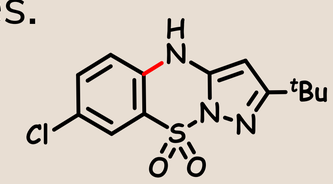


Entry.	X	Conditions	Yield (%)
1	Br	3 eq. KO^{t}Bu, DMSO, 30 min, Green LED.	53
2	Br	3 eq. KO^{t}Bu, DMSO, 30 min, HPI-T	43
3	Br	3 eq. KO^{t}Bu, DMSO, 30 min, White LED	43
4	Br	3 eq. KO^{t}Bu, DMSO, 30 min, Blue LED	50
5	Br	3 eq. KO^{t}Bu, DMSO, 30 min, Dark	X
6	Br	3 eq. KO^{t}Bu, DMSO, 15 min, Green LED	28
7	Br	3 eq. KO^{t}Bu, DMSO, 5 min, Green LED	24
8	Br	3 eq. KO^{t}Bu, DMSO, 5 min, Dark	X

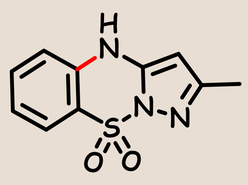
Other conditions



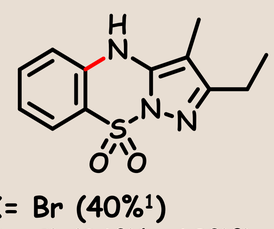
6 Synthetic scope: Benzopyrazolothiadiazines.



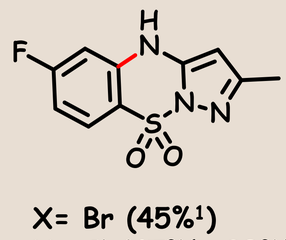
X= Cl (36%)[1]



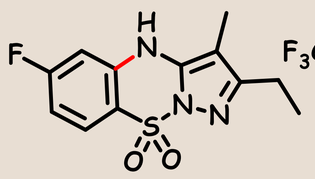
X= Br (53%)[1]
X= Cl (30%)[1]



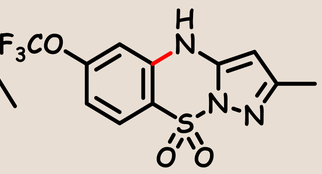
X= Br (40%[1])
X= Cl (26%[1], 10%[2])



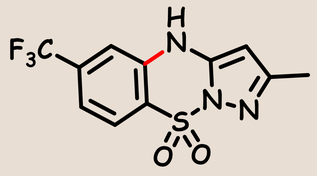
X= Br (45%[1])
X= Cl (47%[1], 20%[2])



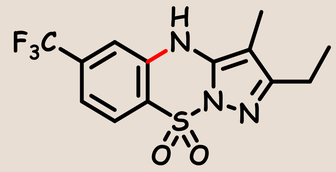
X= Cl (78%)[1]



X= Br (51%)[1]



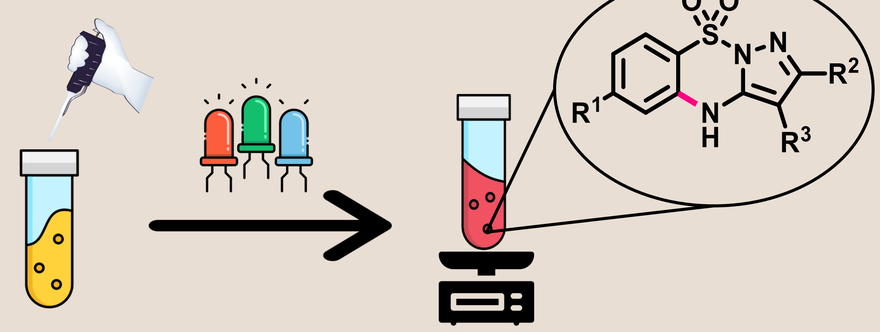
X= Br (50%[1], 27%[2])



X= Br (55%)[1]

[1] Quantified by 1H NMR.
[2] Isolated Reaction Yield.

Experimental procedure.



7 Conclusions.

An innovative synthetic methodology was developed for the preparation of a family of benzopyrazolothiadiazine derivatives, without the need to use metals as catalysts or high temperatures and at very short reaction times. The optimal reaction conditions were identified according to the nature of the substrate. In the case of substrates with X=Br, the best results were obtained with a reaction irradiated by green LED for 30 minutes, using DMSO as solvent and 3 equivalents of KO^{t}Bu.

8 References

1. Chhabra, S. *et al* (**2021**). *Med. Chem.* Res, 30, 15-30; **2**. Plescia, S. *et al* (**1975**). *Heterocyclic. Chem*, 13, 395-401.

Acknowledgements

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