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Convenient synthesis of substituted thiazolo [4,5-b] quinolines

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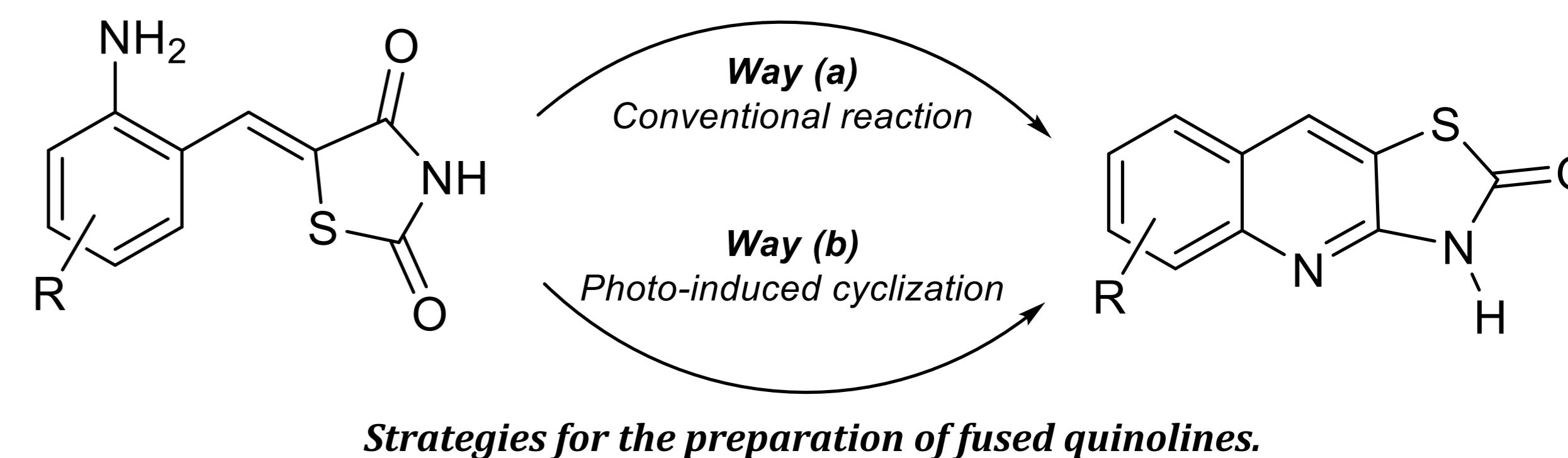
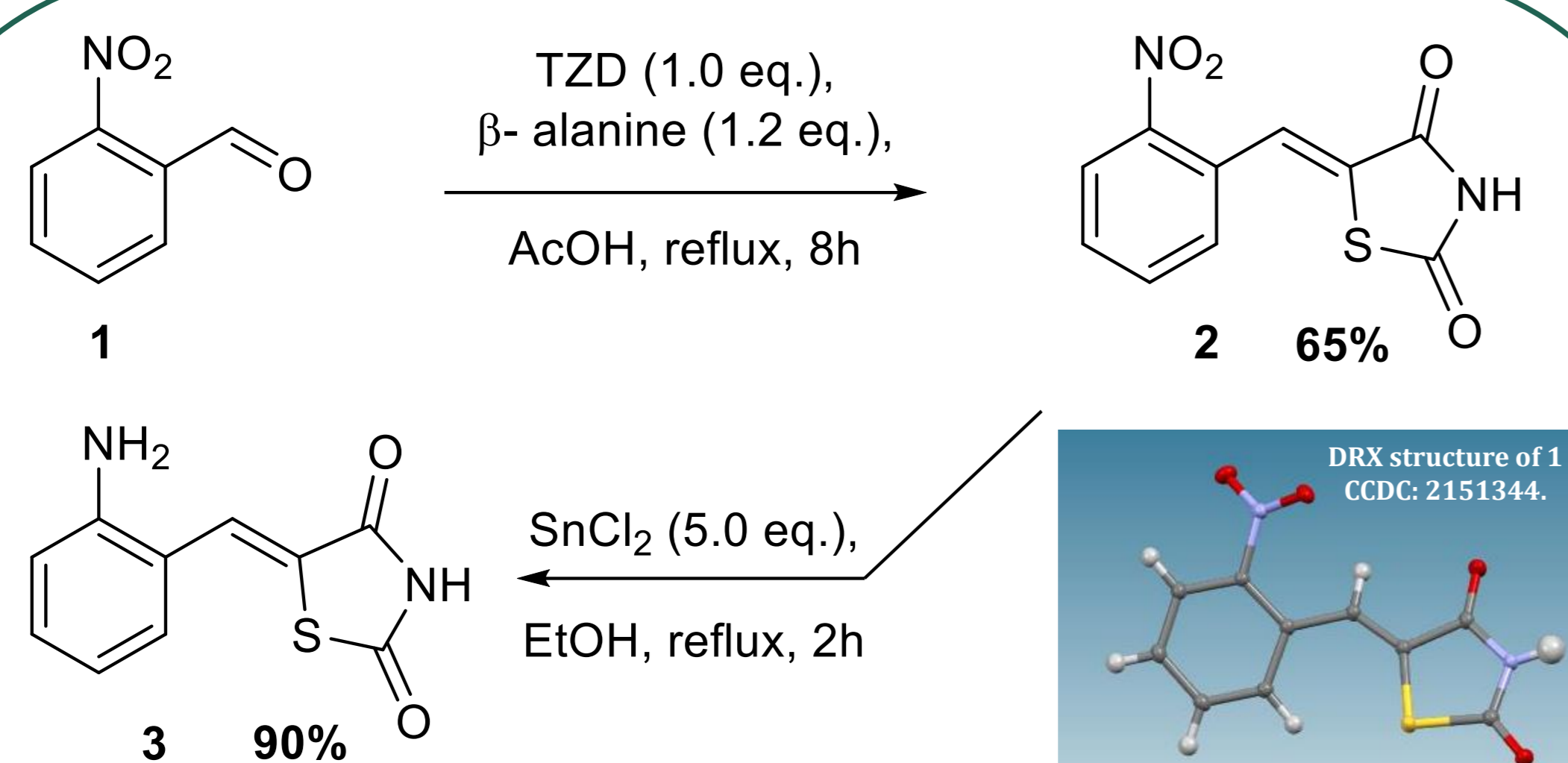
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Introduction

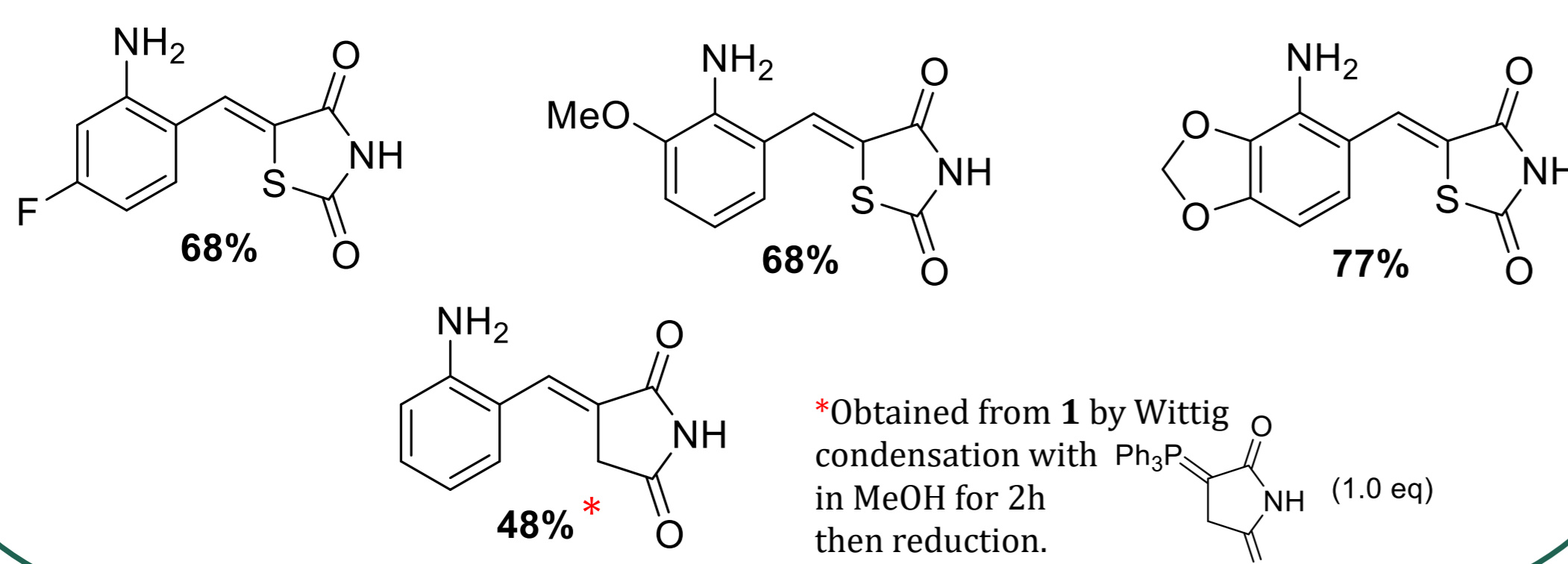
Quinoline structures are interesting as they are present in a large variety of biologically active compounds,¹ thus their synthesis have received a large attention. Many methods are employed to prepare these moieties but they often need hard conditions.^{2,3,4} In this work, we focused our attention on a short and efficient synthesis of fused quinolines. We envisioned two strategies:

- * one with classical conditions,
- * a more original one, based on photo-induction.

Preparation of *o*-aminobenzylidene scaffold

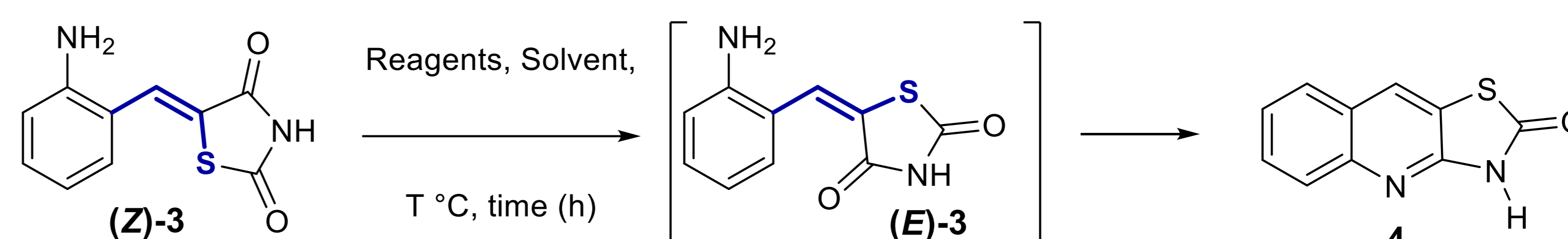
- Easy and fast synthesis.
- Good overall yield (59%).
- Only pure isomer (*Z*) is obtained.

Extension of the sequence to various aminobenzylidenes



Classical way

The preparation of quinoline **4** depends on the isomerization of the double bond.



Conditions for preparation of quinoline **4**.

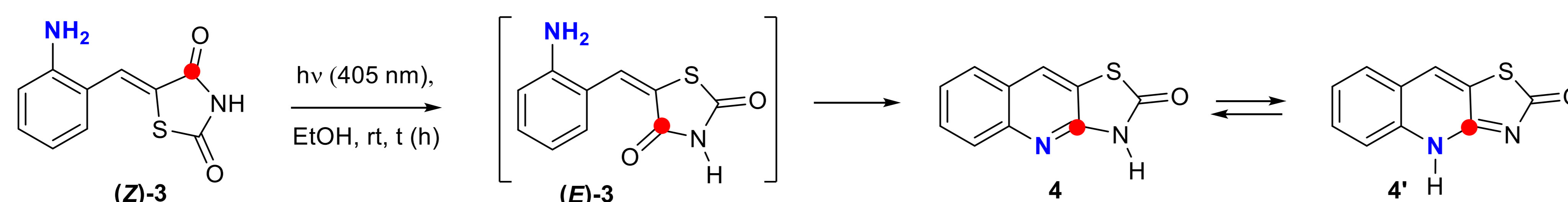
Starting material	Solvent	T (°C)	time	Reagents	Results
	Acetone	r.t.	2 h to 48 h	none	Traces of 4
	Acetone	r.t.	2 months	none	80% of 4
	Acetone	reflux	2 h to 24 h	none	degradation
	Toluene	reflux	3 h to 24 h	APTS (0.1 eq)	s.m. ^c
	EtOH	180°C ^a	3 h	none	degradation
	EtOH	150°C ^a	3 h	none	degradation
	EtOH	120°C ^a	3 h	none	degradation
	EtOH	reflux ^b	8 h	SnCl ₂ (5.0 eq)	3 (90%), 4 (10%) ^d
	EtOH	reflux	8 h	SnCl ₂ (20.0 eq)	3 (90%), 4 (10%) ^d
	EtOH	120°C ^a	3 h	SnCl ₂ (5.0 eq)	degradation

^a Thermal reactions were run in sealed vessel. ^b Under microwaves. ^c s.m. Starting material. ^d Yield estimated by ¹H NMR.

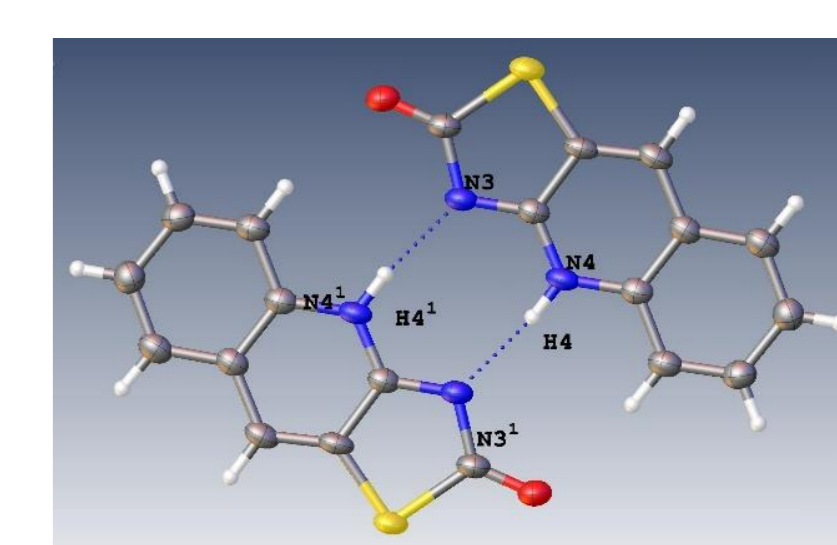
Acid activation **X** High pressure **X** Long time agitation **✓** Light activation ? **⚡**
High temperature **X** Microwaves **X**

Photochemistry way

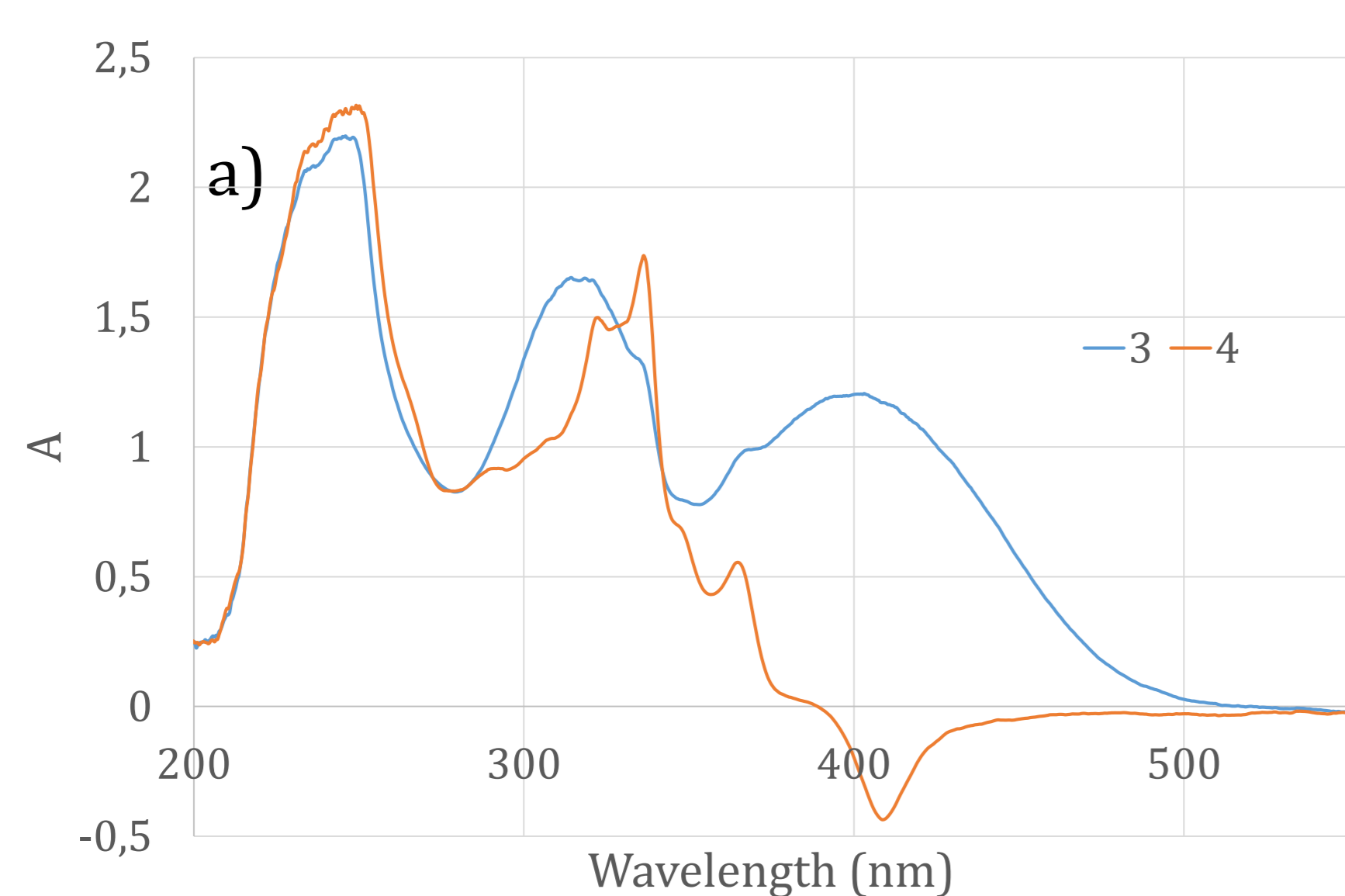
The nucleophilic attack of the amine moiety on a carbonyl group depends on the double bond configuration: an inversion is necessary to obtain the fused quinoline. As a consequence of the latter results (acetone, r.t., 2 months), we investigated the photo-induced isomerization of the double bond with light.^{5,6,7}



Solutions of amine **3** and quinoline **4** in EtOH



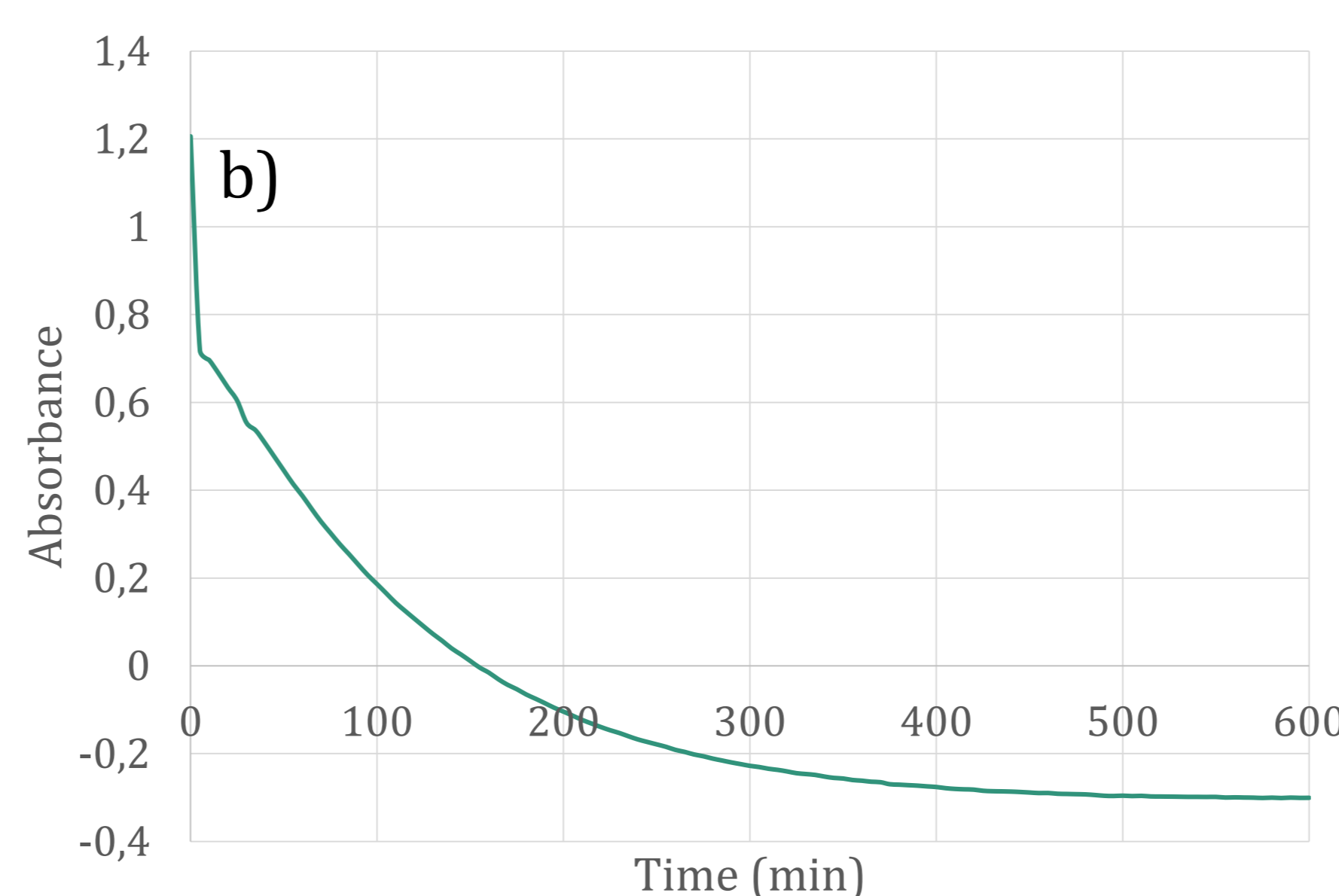
DRX structure of quinoline **4'** CCDC: 2151345.



a) UV-visible spectra of amine **3** and quinoline **4** in EtOH; b) kinetic study of amine **3** consumption under irradiation at 405 nm.

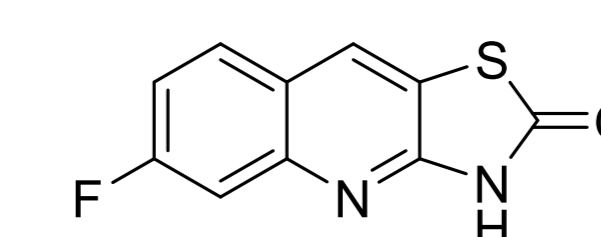
→ Product **4** was prepared after a 48h irradiation at 405 nm in an excellent 84% yield (overall yield 49%).

→ Extension of the photoinduced cyclization sequence afforded various fused azaheterocycles in 48 to 77% yields.

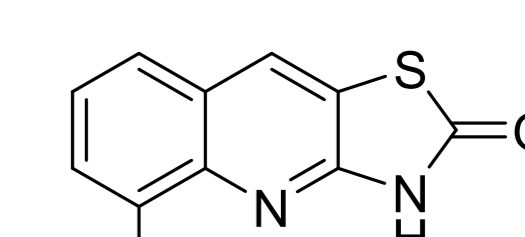


Exemplification

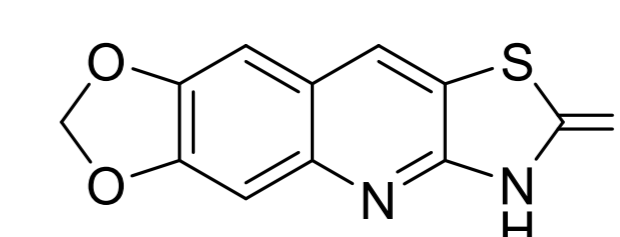
Various fused azaheterocycles were obtained by photoinduction.



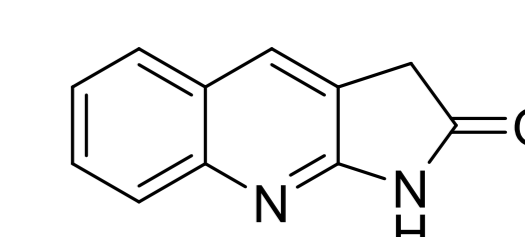
68% $\lambda = 405$ nm
 $t = 48$ h
Overall yield : **33%***



68% $\lambda = 405$ nm
 $t = 48$ h
Overall yield : **39%***



77% $\lambda = 430$ nm
 $t = 48$ h
Overall yield : **18%***



48% $\lambda = 375$ nm
 $t = 48$ h
Overall yield : **30%***

*Overall yield calculated for 3 steps.

Conclusion

We succeeded in preparing various fused quinolines with a 3-steps synthesis in **18 to 49%** overall yields. The first two steps were fast and effective as we obtained amines **3** as pure products in very good yields (**23 to 62%**). The third step consisted in a photo-induced isomerization followed by a subsequent cyclization. This method is convenient, clean and really effective compared to classical ways.⁸

References

- [1] Weyesa, A.; Mulugeta, E., *RSC Adv.* **2010**, *10*, 20784–20793. [2] Mekheimer, R.A.; Al-Sheikh, M. A.; Medrasi, H. Y.; Sadek, K. U., *RSC Adv.* **2020**, *10*, 19867–19935. [3] Ramann, G. A.; Cowen, B. J., *Molecules*, **2016**, *21*, 986. [4] Kouznetsov, V. V.; Vargas Méndez, L. Y.; MeléndezGómez, C. M., *Curr. Org. Chem.* **2005**, *9*, 141–161. [5] Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohma, T., *Chem. Pharm. Bull.* **1991**, *39*, 1440–1445. [6] Murata, M.; Zheng, H.; Chen, L.; Li, R.; He, C.; Yang, S.; Ye, X.; Chen, Z.; Li, Z.; Gao, Y.; Han J.; He, G.; Yang, L.; Wei, Y., *J. Med. Chem.* **1999**, *34*, 1061–1070. [7] Chen, X.; Qiu, S.; Wang, S.; Wang, H.; Zhai, H., *Org. Biomol. Chem.* **2017**, *15*, 6349–6352. [8] Cortelazzo-Polisini, E.; Boisbrun, M.; Gansmüller, A. H.; Comoy, C. *J. Org. Chem.* **2022**, submitted.