PHOTOCHEMICAL SYNTHESIS OF WEINREB AND MORPHOLINE AMIDES

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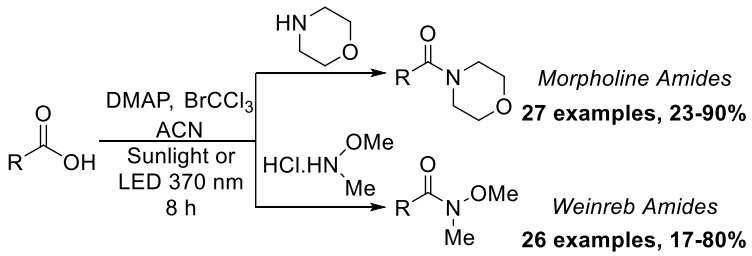
In recent years, light-mediated methods for synthetic routes have attracted the interest of the scientific community, because they constitute alternative and eco-friendly approaches for the production of valuable chemical compounds, such as Weinreb amides and morpholine amides. Both of them find interesting applications in the synthesis of pharmaceutical agents.
In 2021, Szpilman and co-workers demonstrated a sunlight-mediated protocol for the coupling of amino acids to afford peptides, which relies on the light activation of a DMAP–$BrCCl_3$ charge transfer complex (CTC) to generate a novel coupling reagent *in situ*.[1] Based on this, we considered that such a protocol may work for the synthesis of either Weinreb or morpholine amides, but we decided to explore the use of both sunlight and LED lamps as the irradiation source for the light-mediated coupling.
In this study, we demonstrate a photochemical protocol for the synthesis of Weinreb amides and morpholine amides from carboxylic acids. Various carboxylic acids, from aliphatic acids to amino acids, were directly coupled to *N*,*O*-dimethylhydroxylamine or morpholine, upon irradiation with either LED 370 nm or sunlight in the presence of 4-dimethylaminopyridine and bromotrichloromethane, providing Weinreb and morpholine amides respectively, in satisfactory to high yields. Thus, versatile building blocks such as Weinreb amides and morpholine amides may be efficiently synthesized directly from carboxylic acids by light-mediated approaches, without the need of coupling reagents or pre-activation of carboxylic acids.
To our knowledge, this is the first photochemical protocol for the synthesis of Weinreb and morpholine amides, suggesting that synthetic photochemistry may offer alternatives to conventional methods for the synthesis of valuable synthetic intermediates.



References

[1] Mishra A. K.; Parvari G.; Santra S. K.; Bazylevich A.; Dorfman O.; Rahamim J.; Eichen Y.; Szpilman A. M., *Angew. Chem. Int. Ed.* **2021**, *60*, 12406-12412.