PHOTOREDOX-CATALYZED ALKYLATION OF HETEROAROMATIC BASES USING ETHYL ACETATE AS ALKYLATING AGENT

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The direct C-H functionalization of heteroaromatic compounds is an emerging field in modern organic synthesis. Functional group introduction through C-H activation, for instance the Minisci-reaction, needs strong oxidizing agents and high temperature.\(^1\) Solvents having C-H bond adjacent to an oxygen (alcohol, ether or ester) can be cleaved via a hydrogen atom transfer (HAT) process, and the corresponding radical (alkyl group usually) can react with the heteroarene directly, giving benzyl alcohol derivatives. Using alcohols as coupling agents, radical-mediated elimination of H\(_2\)O via a spin-center shift (SCS) followed by a proton-coupled electron transfer (PCET) could alternatively lead to alkylated products instead of hydroxyalkylated derivatives.\(^2,3\)

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\begin{align*}
\text{H} + \text{R} & \xrightarrow{\text{Ir-photocatalyst}} \text{R}\text{O} \\
\text{CSA, PhC(O)O\text{tBu}} & \quad \text{Blue LED, RT} \\
& \uparrow \text{to 82% yield 22 examples}
\end{align*}
\]

Figure 1. Photoredox C(sp\(^2\))-C(sp\(^3\)) cross-dehydrogenative-coupling

Our ongoing research demonstrates, that heteroaromatic rings can be alkylated in radical fashion employing EtOAc both as solvent and alkylating agent under visible-light photoredox conditions. Heterocyclic \(\alpha\)-methyl benzyl alcohol derivatives were obtained by using catalytic amount of camphorsulfonic acid (CSA), TBBP (\(t\text{ert}\)-butyl perbenzoate), \((\text{Ir}[\text{dF(CF}_3\text{ppy})_2(\text{dtbpy})])\text{PF}_6\) as photocatalyst and blue LED-light. Under the optimized conditions 22 compounds were successfully isolated on 2 mmol scale with yields up to 82%. The selected examples mainly consist of quinoline-, isoquinoline- and quinazoline derivatives possessing potential pharmacophore properties. Moreover, our model compound was synthesized on 5 g scale in a yield of 63% demonstrating the robustness of the protocol.

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