Synthesis of 2*H*-1,4-Oxazin-3(4*H*)-one Utilizing Umpolung Reaction to α-Hydrazonoketone

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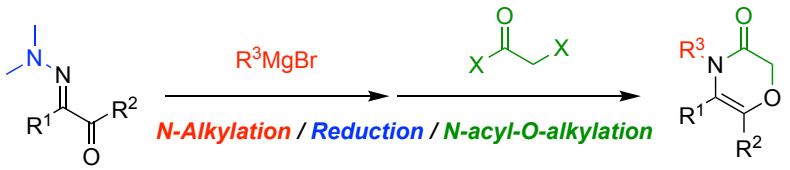
1,4-Oxazine skeletons are 1,4-morpholine precursors which are important frameworks in a variety of biologically active compounds such as Amorolfine (antifungal), (±)-Chelonin C (antibacterial), Reboxetine (antidepressant), Aprepitant (NK1 blocker), and Phendimetrazine (appetite suppressant). 2*H*-1,4-Oxazin-3(4*H*)-one derivatives exhibit a wide spectrum of biological activity such as antifungal, anticancer, antidepressant, as receptor antagonists and potassium channel modulators. Development of synthetic methods for 1,4-oxazine and their derivatives has been intensively explored and many reactions have been reported so far. However, there are still requirements to develop easier and more efficient methods for them.

We have developed tandem reactions utilizing umpolung reactions for α-imino ester analogues and have succeeded in a lot of integrating reactions.[1] We reported the synthesis of tetramic acid derivatives by umpolung *N*-alkylation of γ-hydrazono-β-ketoesters/reduction/cyclization in 2020.[2] We also developed synthesis of *N,N*-dialkylaminoamides via umpolung *N*-alkylation/intramolecular amidation/*N*-alkylation of α-hydrazonoesters in 2021.[3] We found that an α-hydrazonoketone as a new substrate, is an effective one for an umpolung *N*-alkylation followed by an intramolecular hydride reduction and *N*-acyl-*O*-alkylation. These reactions lead to a one pot syntheses of 2*H*-1,4-oxazin-3(4*H*)-one. The *N*-methylation reaction proceeds extremely fast (for only 30 seconds) to afford the *N*-methylated product in a quantitative yield.



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