

Milder Preparation of a γ -Azido- α -diazo- β -keto Ester by Consecutive Introduction of Azido and Diazo Groups

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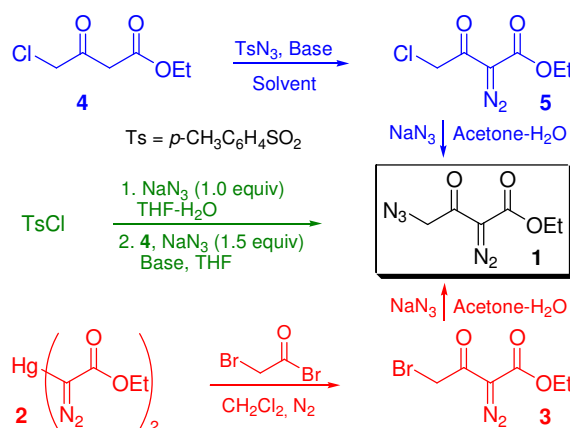
INTRODUCTION

Diazo compounds have been used extensively as precursors of metal carbene intermediates, which can subsequently undergo diverse transformations such as X-H insertion (X = C, O, S, N), and cyclopropanation.¹ Organic azides are valuable intermediates for the synthesis of many nitrogen-containing molecules,² including heterocycles and natural products.³ Although the isoelectronic azido and diazo functionalities are synthetically useful, the chemical behavior of compounds decorated with both azido and diazo groups remains unexplored.⁴

Some years ago, we reported⁵ the synthesis of γ -azido- α -diazo- β -keto esters and the chemoselective transformation of their multiple functional groups that ultimately gave more elaborated structures.⁶ The key azido diazo building block **1** was originally prepared in 2 steps by coupling the diazomercurial **2** with bromoacetyl bromide under anhydrous conditions followed by treating the bromo diazo intermediate **3** with azide anion⁵ (Scheme 1, Red route). Although this methodology furnished the expected product **1** in high yields and mild conditions, the diazomercurial **2** is not commercial and harmful to the health and environment. Herein, we report our initial achievements through a more simple and safe methodology for the synthesis of **1** starting from the commercially available ethyl 4-chloroacetoacetate (**4**) (Scheme 1, Blue route).

RESULTS AND DISCUSSION

The γ -chloro- α -diazo- β -keto ester **5** was prepared from **4** by a diazo transfer reaction using tosyl azide (TsN_3) in basic medium. A variety of conditions was studied, including different combinations of base (triethylamine [TEA], *N*-methylmorpholine, K_2CO_3) and solvent (THF, acetone, acetonitrile). While the use of TEA in THF led to a clean formation of **5**, the recovery mass was consistently low, possibly due to an extensive loss of product during the aqueous work-up. More promising results were achieved with the bulkier base *N,N*-diisopropylethylamine (DIPEA) in THF for 24 h followed by quenching the reaction with HCl before the basic aqueous work-up, giving the chloro diazo ester **5** in 50-70% yield.



Scheme 1. Preparation of azido diazo ester **1**.

The subsequent preparation of azido diazo ester **1** from **5** by chlorine displacement with azide in aqueous acetone for 24 h gave the expected product in high yield. Diazo compounds **1** and **5** were characterized by IR and ^1H NMR, and their spectroscopic data were in agreement with those already published.⁵

Finally, preliminary results indicated that azido diazo ester **1** can be prepared in one pot from **4** and tosyl chloride, by first generating TsN_3 *in situ* followed by consecutive diazo transfer and displacement with azide (Scheme 1, Green route).

CONCLUSION

Preparation of azido diazo ester **1** from **4** by a diazo transfer reaction and subsequent nucleophilic displacement is a promising methodology. This simple protocol can be adapted to a one-pot process without isolation of any intermediates. Further studies are in progress to optimize the reaction conditions.

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UFSC, CAPES, CNPq, FAPESC

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