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

Luiz Gustavo Dutra (PG),* Marcus Mandolesi Sá (PQ)

Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis/SC, 88040-900, Brasil

*Corresponding author. Tel. +55-48-37219967; Fax: +55-48-37216850
"e-mail: dutralg@yahoo.com.br

Keywords: Azido esters, Diazo carbonyl, Diazo transfer

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. Organic azides are valuable intermediates for the synthesis of many nitrogen-containing molecules, including heterocycles and natural products. Although the isoelectronic azido and diazo functionalities are synthetically useful, the chemical behavior of compounds decorated with both azido and diazo groups remains unexplored.

Some years ago, we reported 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. The key azido diazo building block was originally prepared in 2 steps by coupling the diazomercurial 1 with bromoacetyl bromide under anhydrous conditions followed by treating the bromo diazo intermediate with azide anion (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 (TsN₂) in basic medium. A variety of conditions was studied, including different combinations of base (triethylamine [TEA], N-methylmorpholine, K₂CO₃) 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-dissopropylethylamine (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.

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. Diazocompounds 1 and 5 were characterized by IR and 1H NMR, and their spectroscopic data were in agreement with those already published.

Finally, preliminary results indicated that azido diazo ester 1 can be prepared in one pot from 4 and tosyl chloride, by first generating TsN₂ 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.

ACKNOWLEDGEMENTS

UFSC, CAPES, CNPq, FAPESC

REFERENCES