Tetrahedron Letters,Vol.28,No.44,pp 5351-5352,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

RHODIUM CARBENOID MEDIATED CYCLISATIONS. USE OF ETHYL LITHIODIAZOACETATE IN THE PREPARATION OF ω-HYDROXY-, -MERCAPTO-, AND -Boc-AMINO-α-DIAZO-β-KETO ESTERS

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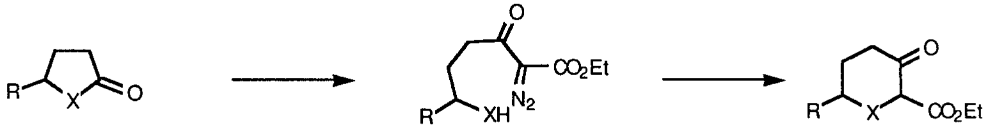
Summary: Reaction of ethyl lithiodiazoacetate with lactones, thiolactones, and lactams (**1**, **4**, **8**) gives the diazo-compounds (**2**, **5**, **9**), substrates for rhodium carbenoid cyclisation reactions.

The role of diazo-carbonyl compounds in organic synthesis is well established,[1] and in recent years much effort has been devoted to the study of the effect of different transition-metal catalysts on these reactions.[2] However, in synthetic terms, most of the work has centred on the cyclopropanation and C-H insertion reactions of the resulting carbenes or metallocarbenoids; very little attention has been paid to the formation of C-hetero atom bonds. Recently we reported the use of a rhodium (II) acetate mediated cyclisation reaction of ω-hydroxy-α-diazo-β-keto esters to give 7- and 8-membered ring ethers.[3] At about the same time, Rapoport's group described the preparation of 4-, 5-, and 6-membered ring nitrogen heterocycles, and 5-membered ring ethers and thioethers using similar chemistry.[4] We now report a new one step route to ω-hydroxy, -mercapto, and Boc-amino-α-diazo-β-keto esters, the precursors for the rhodium carbenoid mediated cyclisation reactions, using ethyl lithiodiazoacetate.[5]

Commercially available ethyl diazoacetate (EDA) can be readily lithiated at low temperature, and the resulting organometallic is known to undergo addition to ketones.[5] It occurred to us that if the anion were to add to lactones, it would constitute a simple one step route to ω-hydroxy-α-diazo-β-keto esters, the substrates for cyclisation which we had previously prepared by a 3 step sequence. In the event, metallation of EDA with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at -90°C followed by quenching with γ-valerolactone (**1a**) gave the diazo alcohol (**2a**) (51%). Alternatively the reaction could be carried out by addition of a solution of LDA to a mixture of EDA and the lactone in THF at -78°C. In a similar manner, reaction of ethyl lithiodiazoacetate with the lactones (**4a**), (**4b**), and (**8**) gave the diazoalcohols (**5a**), (**5b**), and (**9**) in 76, 88, and 56% yield respectively. The anion reaction could also be extended to the opening of thiolactones (**1b**) (76% crude) and (**4c**) (52%), the *N*-Boc lactam (**4d**) (60%), 1,3-dioxan-2-one (37%), and glutaric anhydride (36%). α,β-Unsaturated lactones, lactones with more acidic α-protons (*e.g.* isochroman-3-one), and *N*-methyl lactams were very poor electrophiles for ethyl lithiodiazoacetate.

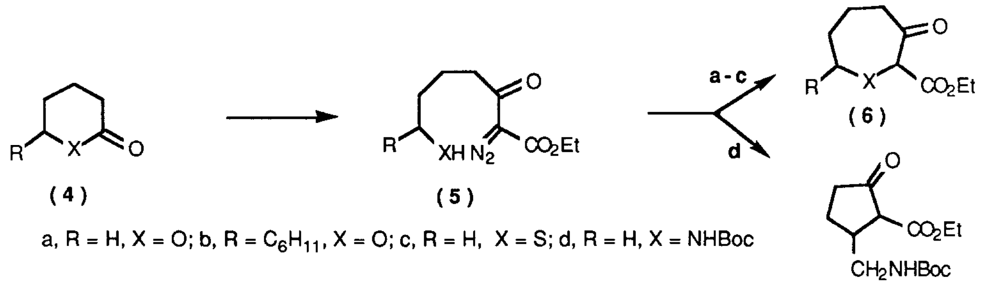
On treatment with rhodium (II) acetate in benzene (or dichloromethane), the diazo alcohols (**2a**), (**5a**), (**5b**), and (**9**) cyclised to the corresponding cyclic ethers (**3a**) (80%), (**6a**) (64%), (**6b**) (39%), and (**10**) (12%). Similarly the diazo thiols (**2b**) and

(**5c**) cyclised to the cyclic thioethers (**3b**) and (**6c**) although in lowish yield (30-35%). The yield of the benzo-fused 8-membered ether (**10**) was particularly low; the major product was the cyclopentanone (**11**) (69%), formed by competing C-H insertion at the benzylic position. However, the yield of the benzoxocane (**10**) could be improved to 32%, at the expense of the cyclopentanone (**11**) (34%), by using rhodium (II) trifluoroacetate as the catalyst. In the case of the diazo *t*-butylcarbamate (**5d**), the only observed reaction was C-H insertion to give the cyclopentanone (**7**) (73%); presumably the Boc-protected nitrogen is not sufficienly nucleophilic to intercept the electrophilic rhodium carbenoid intermediate.



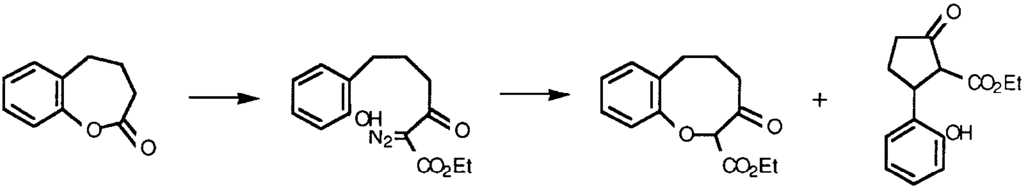
(**1**) (**2**) (**3**)

a, R = Me, X = O; b, R = H, X = S



(**4**) (**5**) (**6**) (**7**)

a, R = H, X = O; b, R = C_6H_{11}, X = O; c, R = H, X = S; d, R = H, X = NHBoc



(**8**) (**9**) (**10**) (**11**)

Acknowledgements

We thank the S.E.R.C. for a studentship (to R.J.T.) and the Royal Society of Chemistry for a Hickinbottom Fellowship (to C. J. M.).

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(Received in UK 21 August 1987)