Pergamon

*Tetrahedron Letters*, Vol. 38, No. 14, pp. 2551-2552, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00398-5

# Efficient Conjugate Addition of Hydrogen Azide to Enoates

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***Abstract*** : A simple and efficient conjugate addition of hydrogen azide to enoates is described.

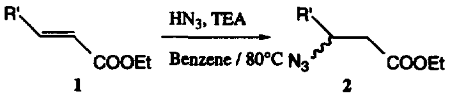
Oliveri-Mandala[1] in 1915 reported the formation of azido hydroquinone by the addition of hydrogen azide to benzoquinone. This appears to be the first reported example of the formation of an organic azide by the addition of hydrogen azide to a conjugated system. Later in 1951 J.H. Boyer[2] reported additional examples in which certain limitations were also discussed. Further, conjugate addition of hydrogen azide to the α,β-unsaturated carbonyl compounds reported so far has been mainly studied in acidic media (i.e. aqueous AcOH, $CHCl_3$-AcOH-$CCl_3COOH$)[3] but only with poor results. Recently B.Y. Chung et al[4] have reported milder reaction conditions at the expense of diethyl aluminium azide to give moderate yields. We report herein an efficient base catalysed addittion of hydrogen azide to enoates to form β-azido esters or lactones at ambient temperatures.

β-Amino esters and lactones are vital constituents of many natural products. A common synthetic strategy to prepare β-amino carbonyl compounds is the conjugate addition of nitrogen nucleophile to the α, β-unsaturated carbonyl compounds. As part of our ongoing research to synthesize Obscurolides,[5] a phosphodiesterase inhibitor, we wanted to prepare a β-azido lactone under near neutral conditions to avoid the cleavage of acid labile protecting groups.

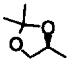
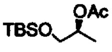
When we attempted the reaction with preformed hydrazoic acid solution in benzene,[6] no product was formed and the starting material was recovered. Under phase transfer catalysed conditions, the reaction was slow and the prolonged reaction period gave only poor yields. At this stage we attempted base catalysed Michael type addition to overcome this problem. Surprisingly in the presence of quaternisable bases such as triethylamine and pyridine the reaction proceeded smoothly without affecting the acid cleavable protecting groups. Of the several bases tried triethylamine gave better yields. At ambient temperatures and with catalytic amounts of base the reaction went to completion to give excellent yields. Some representative examples of the present reaction are given in Schemes 1 & 2.

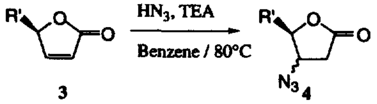
It can be seen from the table that chiral substrates exhibit stereoselectivity in the product formation (1E and 2B). Azido compound **4B** was compared with the literature report.[8] The isomers of compound **2E** were converted to known compounds by the two step hydrogenation-benzylation process and compared against the reported results.[9] Further investigations are in progress to improve the diastereoselectivity and also to devise an enantioselective azidation reaction.

In summary the present reaction with its mild reaction conditions opens a novel entry to the direct conjugate addition of hydrogen azide to enoates.



**Scheme 1**

| 1 - 2 | R' | Reaction time(h) | Yield[a/b]( syn / anti )[c] (%) |
|---|---|---|---|
| A[f] | H - | 8 | 90 |
| B[d, f] | $CH_3$ - | 24 | 96 |
| C[d] | $PhCH_2$ - | 24 | 90 |
| D | $BnOCH_2$ - | 15 | 97 |
| E |  | 6 | 98 ( 1/2 ) |
| F |  | 18 | 95 ( 1/1 ) |



**Scheme 2**

| 3 - 4 | R' | Reaction time(h) | Yield[a/b]( syn / anti )[c] (%) |
|---|---|---|---|
| A[f] | H - | 5 | 90 |
| B[e] | $TrOCH_2$ - | 24 | 70 (1/100 ) |

a) All the new compounds described herein gave spectral data consistent with the assigned structures; b) Isolated yields are based on the starting olefin; c) Determined by HPLC/$^1H$ NMR; d) 2 equivalents of base was used; e) This reaction was done at room temperature; f) These products were reduced and suitably protected to give N-protected β-amino esters and compared against the reported results[7].

A typical experimental procedure is exemplified as follows: A solution of compound **1** (10 mmol), $HN_3$ (150 mmol, 2M solution in benzene) and triethylamine (1 mmol) in benzene was stirred at 80°C. After completion of the reaction (monitored by TLC), washing with water, drying over anhydrous $Na_2SO_4$ and concentrating in vacuo gave crude product **2** which was purified by column chromatography using $SiO_2$.

**Acknowledgments** : One of the authors (P.L. Pathi) thanks Dr A. Dutta for helpful discussions and CSIR, New Delhi for financial support.

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IICT Communication No. 3778.

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(*Received in UK* 17 *January* 1997; *revised* 26 *February* 1997; *accepted* 28 *February* 1997)