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LETTERS

Alkylation of Ketone and Ester Lithium Enolates with Nitroethylene

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Abstract: Nitroethylene is a "${}^{+}CH_2CH_2NH_2$" and "${}^{+}CH_2CHO$" synthon which has not been widely used in conjugate addition reactions, due in part to its reputation for facile anionic polymerization. In the present report, we describe the first systematic study of the scope and limitations of the conjugate addition of ketone and ester enolates to nitroethylene. Synthetically useful yields are obtained for ketone and ester enolates of a variety of structural types.

Nitroolefins are powerful Michael acceptors which can serve as synthons of the types "${}^{+}C\text{-}C\text{-}NH_2$" and "${}^{+}C\text{-}(C{=}O)R$" [2,3]. Historically, the utility of nitroolefins in conjugate addition reactions has been limited by their facile polymerization in the presence of nucleophiles. In recent years Yoshikoshi [4], Seebach [5-10], Denmark [11-13], and others [14-16] have reported procedures for the successful addition of ketones to nitroolefins via their lithium enolates, enol silanes, enol ethers, or enamines. Likewise, esters have been successfully added to nitroolefins via their lithium enolates or ketene silyl acetals [3,16]. Despite these successes, only a handful of reports exist concerning the addition of enolates to the most reactive simple nitroolefin, nitroethylene [17-21]. The synthetic utility of this reagent in conjugate addition reactions therefore remains poorly defined.

Table 1 describes the results of our investigation into the alkylation of ketone lithium enolates with nitroethylene. Also shown in the table is an example of this reaction which was previously reported by others [22]. With the exception of entry 4, ketone enolates having a single alkyl substituent on the nucleophilic carbon gave 46-74% yields of the corresponding conjugate addition products. Two enolates that are disubstituted on the nucleophilic carbon were also examined in this study (entries 8 and 9). A 58% yield was obtained in the reaction described by entry 8, but an accurate yield could not be determined for entry 9 due to

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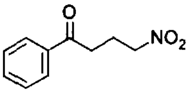
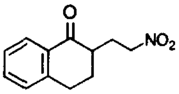
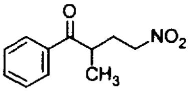
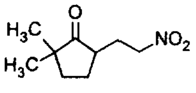
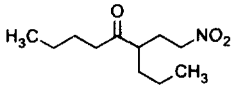
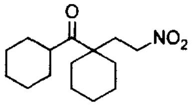
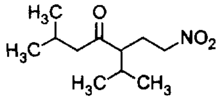
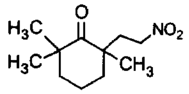
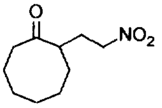
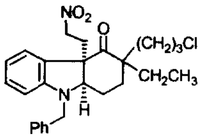
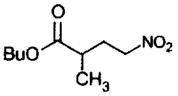
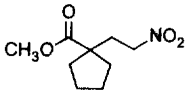
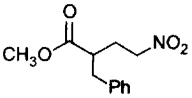
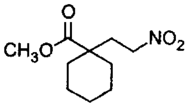
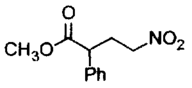
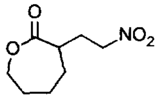
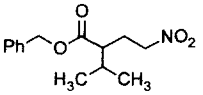
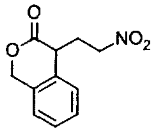
Table 1. Alkylation of ketone enolates with nitroethylene.

Entry	Product	Yield[a]	Entry	Product	Yield[a]
1		61%	6		74%
2		74%	7		67%
3		46%	8		58%[c]
4		< 50%[b]	9		< 46%[b]
5		72%	10		62%[d]

[a]All new compounds gave satisfactory ^{1}H-NMR, MS, and CHN data except where noted. [b]Indicated upper limit is the nominal yield of a chromatographed product which failed to give a satisfactory CHN analysis. [c]Calculated yield corrected for recovered starting ketone. [d]Ref. 22.

Table 2. Alkylation of ester enolates with nitroethylene.

Entry	Product	Yield[a]	Entry	Product	Yield[a]
1		59%	5		94%
2		57%	6		75%
3		99%	7		50%
4		77%	8		75%

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[a]All new compounds gave satisfactory ^{1}H-NMR, IR, MS, and CHN.

purification difficulties. These results may be compared with that of Benchekroun-Mounir *et al.* who reported a 62% yield for this reaction in the case of the α,α-disubstituted ketone of entry 10 [22].

Table 2 describes our results for the alkylation of ester and lactone lithium enolates with nitroethylene. In accord with expectations based on the greater nucleophilicity of ester enolates, these reactions typically proceed in somewhat higher yields than those of ketone enolates. Ester enolates that are substituted on the nucleophilic carbon with a single branched or unbranched alkyl group or with two unbranched alkyl groups all gave alkylation products in 57-99% yield. The two lactone enolates which were examined in this work gave 50-75% yields.

An unexpected trend in the data shown in Table 2 is a modest direct (not inverse) correlation between the yield of the reaction and the steric hinderance of the nucleophilic carbon of the starting ester enolate. A possible explanation for this trend was suggested by the apparent decomposition of the product from Table 1 entry 7 during an attempted chromatography on a high activity silica gel HPLC column. This observation suggests that the relative yields described in Tables 1 and 2 may reflect the effects of both the intrinsic yield of the reaction and a low degree of decomposition of the product during routine purification by flash chromatography. The presence of bulky substituents alpha to the carbonyl group could plausibly retard this unknown decomposition process. Alternatively, the counter-intuitive effect of steric hinderance on the yields of these reactions may reflect differing aggregation states of the starting enolates [23].

General procedure for the alkylation of ketones and esters with nitroethylene. A 25 °C solution of the ketone or ester (1.80 mmol) in 1.5 mL of THF was added dropwise over 3 min to a -78 °C solution of 2.07 mmol lithium diisopropylamide and 0.18 mmol diisopropylamine in 4.5 mL of 2 : 1 THF/hexanes. The mixture was stirred for 1 hour at -78°C. A -78 °C solution of 2.16 mmol nitroethylene [24, 25] in 1.5 mL THF was added dropwise over a 3 minute interval. The reaction mixture was stirred an additional 5 min at -78 °C and then it was then allowed to warm to room temperature over 30 min. The mixture was washed with a large excess of an aqueous solution of sodium dihydrogen phosphate (pH 4). The aqueous phase was washed with dichloromethane. The organic phases were combined and dried ($CaCl_2$). The solvent was evaporated *in vacuo* and the product was isolated by flash chromatography eluting with a mixture of dichloromethane and hexanes.

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23. When the reaction described in entry 2 of Table 2 was performed using the lithium salt of 2,2,6,6-tetramethylpiperidine as base, only traces of the desired conjugate addition product were obtained.
24. Nitroethylene was prepared according to Buckley, G. D.; Scaife, C. W. *J. Chem. Soc.* **1947**, 1471. Best results were obtained when nitroethylene was distilled from the nitroethanol/phthalic anhydride mixture over a period of about 45 minutes. The crude nitroethylene was redistilled at 45 °C/80 torr. Older bottles of nitroethanol which had turned dark gave a product which could not readily be purified. Nitroethylene appears to be stable for several months when stored in the dark at -15 °C. The bottle should be returned to the freezer promptly after transfer of the required amount.
25. In the reaction described by entry 10 of Table 2, addition of a 25 °C solution of nitroethylene gave results similar to those obtained with a -78 °C solution of nitroethylene.