Tetrahedron Letters,Vol.24,No 36,pp 3841-3844,1983
Printed in Great Britain
0040-4039/83 $3.00 + .00

ORGANIC REACTIONS AT HIGH PRESSURE. MICHAEL ADDITION OF ACTIVATED ACYCLIC DONORS WITH β,β-DISUBSTITUTED ENONE ACCEPTORS.[1]

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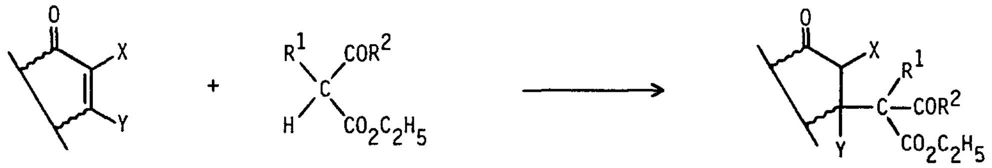
Abstract High pressure, 15 kbar (1.5 GPa), Michael additions of doubly activated acyclic donors to sterically hindered enone acceptors with 1,5-diazabicyclo[4.3.0]non-5-ene in acetonitrile affords Michael adducts in 42-82% yield.

Formation of molecules possessing contiguous quaternary centers by the Michael reaction is limited due to the inability of sterically congested donors and acceptors to undergo condensation.[2,3] Michael additions conducted in aprotic media employing weak bases, catalysts,[4] and directing groups[5] avoid undesirable side-reactions inherent to classical Michael-type protic solvent conditions,[2a] however, these modifications are inefficacious in overcoming steric hindrance Nevertheless, routine success of sterically limited Michael condensations is achieved by using high pressure and aprotic reaction conditions. Matsumoto[6] has shown that substrates which either fail to react or react slowly at ambient pressure undergo Michael additions at 10 kbar. Recently, work in this laboratory has revealed that sterically hindered activated cycloalkanone donors, i e., β-keto esters or 1,3-cyclic diones, and enone acceptors including mesityl oxide react via Michael initiated condensative cyclizations at 15 kbar pressure when either triethylamine or 1,5-diazabicyclo[4.3 0]non-5-ene (DBN) is utilized as base in acetonitrile solvent [7]

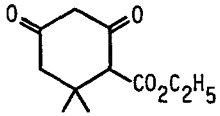


$X = H, Y = CH_3$
$X = CH_3, Y = H$
$X, Y = CH_3$
$X, Y = -(CH_2)_3-$

$R^1 = H$ or CH_3
$R^2 = CH_3$ or OC_2H_5

We report in this communication high pressure Michael additions of acyclic activated donors, diethylmalonate, diethyl methylmalonate, and ethyl 2-methylacetoacetate, with the sterically demanding enone acceptors **1**-**6** (Table I). The high pressure, 15 kbar (1.5 GPa), Michael condensations[8] summarized in Table I were carried out by treating acceptor (1.0 mmol) with donor (1.0 mmol) and DBN[9] (1.5 mmol) in acetonitrile (3 5 mL/mmol) at the temperatures and times indicated. Depressurization, followed by concentration, afforded crude mixtures which were diluted with diethyl ether and washed with water. The ether portions were dried ($MgSO_4$), concentrated and then chromatographed[10] to yield the corresponding Michael adducts **7**-**12**. Under optimal conditions, 45 °C and 15 kbar pressure, products with two contiguous quaternary centers were formed. Temperature dependent studies involving reaction of acceptors and donors for the formation of products **7b**, **7c**, **10b**, **12b**, and **12c** at 15 kbar, 25 °C, for 48 h revealed either incomplete (≤20%) or no reaction of starting materials by ^{1}H NMR analysis.

Ambient (1 bar) pressure control experiments for entries 1-6 performed by reaction of the acceptor (1.0 mmol), donor (1.0 mmol) and DBN (1.5 mmol) in refluxing acetonitrile (3.5 mL/mmol) for 24 h indicated little (<10%) or no formation of Michael adducts **7**-**12** by GC and ^{1}H NMR analyses. These experiments demonstrate that the mild aprotic conditions necessitate the use of elevated pressure to effect Michael condensation. All the ketones obtained in this study are the primary Michael addition products. In contrast, when the starting materials used for the preparation of ketones **7a**, **7b**, **8a**, and **10a** are allowed to react with sodium ethoxide in refluxing ethanol, only the cyclic ketones **13**-**16** are isolated, respectively.[2a,11] Thus, the mild reaction conditions used under high pressure permit control of the reaction sequence.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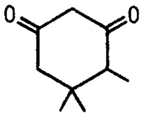
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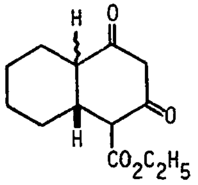
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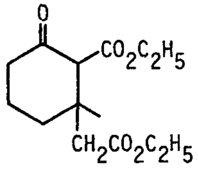
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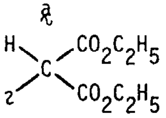
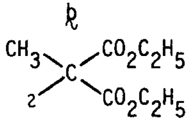
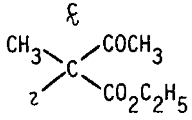
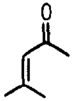
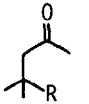
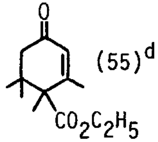
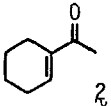
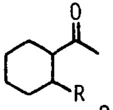
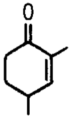
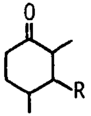
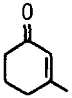
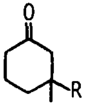
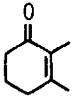
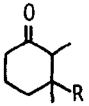
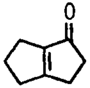
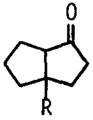
Ethoxide control experiments at 1 bar pressure in which enones **2**[11c] and **4**[11d] were allowed to react with sodium diethylmalonate in ethanol at 25 °C, 24 h, afforded only recovered donor and acceptor starting materials. Heating these mixtures at reflux, 24 h, produced the expected Michael initiated cycloalkanones **15** and **16**, respectively. When enone **4** and sodium diethylmalonate were allowed to react in ethanol at 15 kbar, 25 °C, 48 h, condensation

Table I. Michael addition of doubly activated acyclic donors to α,β-unsaturated ketone acceptors at 15 kbar.[a]

Entry	Acceptor	Product	Donors		
			a R = 	b R = 	c R = 
1	 1	 7	7a(68)[b]	7b(73)[c]	7c  (55)[d]
2	 2	 8	8a(60)[b]	8b(44)[d,e]	complex mixture[d]
3	 3	 9	9a(76)[b]	9b(71)[b]	9c(0)[c]
4	 4	 10	10a(71)[b]	10b(50)[c,e,f]	complex mixture[c]
5	 5	 11	11a(42)[d,e]	11b(0)[d,e]	11c(0)[d,e]
6	 6	 12	12a(82)[b]	12b(77)[d]	12c(58)[d,f]

[a] Yields are isolated. All products gave satisfactory spectral data. [b] 15 kbar, 25 °C, 48 h. [c] 15 kbar, 45 °C, 36 h. [d] 15 kbar, 45 °C, 48 h. [e] Starting materials recovered. [f] Decomposes upon chromatographic purification.

products **10a** and **15** were not observed. Furthermore, the increasingly hindered sodium diethyl methylmalonate when allowed to react with enones **2** and **4** at 1 bar pressure, reflux, 24 h, also failed to afford any of the respective Michael adducts, **8b** and **10b** or the methyl analogues of **15** and **16**. The inability of ethoxide conditions to yield the simple Michael products (Table I) further supports the notion that high pressure and aprotic media are required for the routine success of the Michael condensation with sterically demanding substrates.

In conclusion, high pressure effectively overcomes the steric hindrance imposed by increased substitution near the donor and acceptor reacting centers thereby affording Michael addition products in the yields of 42-82%. Requisite heating at 45 °C, 15 kbar pressure, produces those adducts containing two contiguous quaternary centers Furthermore, these aprotic conditions at high pressure are sufficiently mild to inhibit subsequent cyclizations and rearrangements with the exception of product **7c**.

References and Notes

1. This study was supported by the National Science Foundation, Grant CHE-810-2938.
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3. (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419, (b) Ref. 3a, p. 435.
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8. For a description of the high pressure methodology used, see: Dauben, W. G., Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 282
9. Michael additions at 15 kbar (25 °C and 45 °C) using triethylamine as base failed to afford the desired Michael adducts. The increased effective base strength of DBN at high pressure is discussed in Ref. 7.
10. Short path column chromatography, silica 30-200 mesh; diethyl ether/hexane elution.
11. (a) Steiner, U , Willholm, B. *Helv. Chim. Acta* **1952**, *35*, 1752, (b) Crossley, A. W. *J. Chem. Soc.* **1901**, *79*, 138, *Proc. Chem Soc.* **1900**, *16*, 90, (c) Kon, G.A.R., Qudrat-I-Khuda, M. *J. Chem. Soc.* **1926**, 3071, (d) Farmer, E. H., Ross, J. *J Chem. Soc.* **1925**, *127*, 2358.

(Received in USA 21 June 1983)