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Enamine Chemistry I. Carbanion Alkylations

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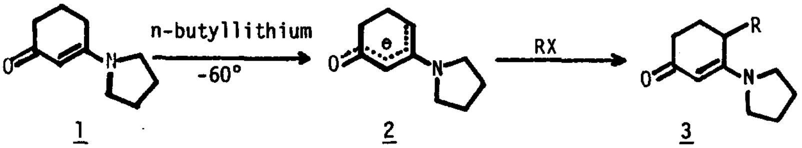
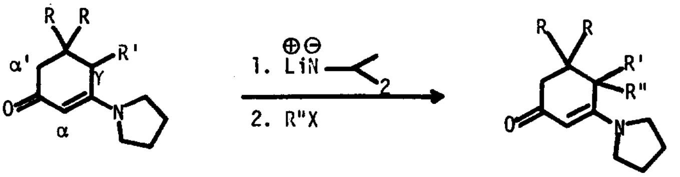
Enaminoketones or vinylogous amides have been used as key intermediates in a variety of synthetic investigations[1] lending importance to a recent study of carbanion alkylation of these systems.[2] In this latter study enaminoketones such as 1 were converted into their extended enolate (2, with n-butyllithium in THF) and alkylated with a variety of alkylating agents, affording the product of exclusive γ-alkylation (3). We have also been investigating this same type of reaction process on a series of enaminoketones, esters and nitriles and have come to the same conclusion; i.e. the carbanion alkylation of these systems results in γ-carbon-carbon bond formation with alkylating and condensation agents. There are some novel and potentially useful aspects of this process that we wish to report herein.



First, this γ-alkylation process is insensitive to substitution at, or near, the position where this new carbon-carbon bond is formed. For example, vinylogous amide 4 with a 4-methyl or 4-(3-methyl-2-butenyl) substituent when treated with lithium diisopropylamide(-78°,THF) and then an alkylating agent undergoes gamma-carbanion alkylation to 5 in good yield with no indications of products resulting from α or α' alkylations. Similar high yields of γ-alkylation products have been observed, by us and by Yoshimoto, Ishida and Hiraoka,[2] when enaminoketone 4d, containing a gem-dimethyl group adjacent to the gamma position, was converted to its anion and treated with alkylating agents (for example forming 5d). The site of alkylation was readily apparent from the ir, UV [enaminoketone chromophore still present; λ_{max}^{EtOH} = ∿300 nm; ir ($CHCl_3$) ∿1550, 1600 cm^{-1}] and pmr (vinylproton, $\delta_{CDCl_3}^{TMS}$ = ∿5.00).[2,3]

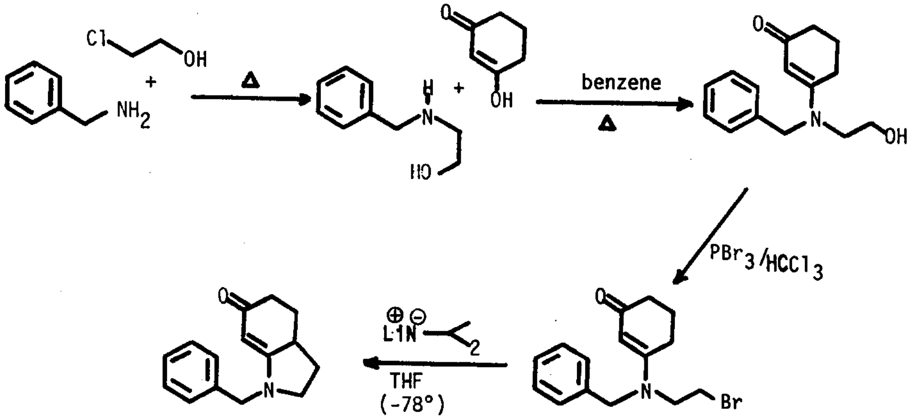


4a, $R=H,\ R'=CH_3$
4b, $R=H,\ R'=CH_3$
4c, $R=H,\ R'=-CH_2CH=C(CH_3)_3$
4d, $R=CH_3,\ R'=H$

5a, $R-H,\ R'-R''=CH_3$
5b, $R=H,\ R'=CH_3,\ R''=CH_2CH=\overset{Cl}{C}-CH_3$
5c, $R=H,\ R'=R''=CH_2CH=C(CH_3)_2$
5d, $R=CH_3,\ R'=H,\ R''-CH_3$

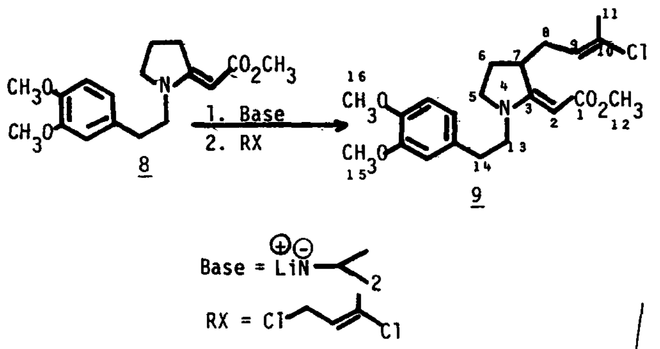
Secondly, a further novel permutation of the γ-alkylation of enaminoketones evolves from our studies of halide 6 which was prepared as shown in Scheme I. Treatment of the enaminoketone 6 with lithium diisopropylamide (1.1 eq.) in THF (-78°) effects intramolecular γ-alkylation forming N-benzyl-2,3,3a,4-tetrahydro-6(5H)-oxoindole [7; λ_{max}^{EtOH} = 299 nm; ir ($CHCl_3$) = 1590 (broad) cm^{-1}; m/e = 227; $\delta_{CDCl_3}^{TMS}$ = 7.25 (m, 5H, AR-H), 5.15 (s, 1H, C_7 H's), 4.3 (s, 2H, C_8 H's), 3.25-3.70 (m, 2H, C_2H's), 1.1-2.9 (m, 7H C_3H, C_{3a} H, C_4 H's, C_5 H's] in good yield.[6] Clearly this intramolecular heterocyclic ring formation opens some interesting approaches to alkaloid synthesis.[4]

Scheme I

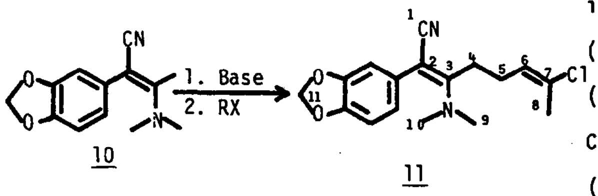


7 6

Thirdly, it is not clear to us why γ-alkylation predominates with enaminoketones while other analogous oxygen and carbon systems undergo α and α'-alkylations,[5] but the same γ-bond formation occurs with simple[2] and complex enaminoesters (i.e. 8 → 9 below) as well as with enaminonitriles (i.e. 10 → 11 below).[7,8]



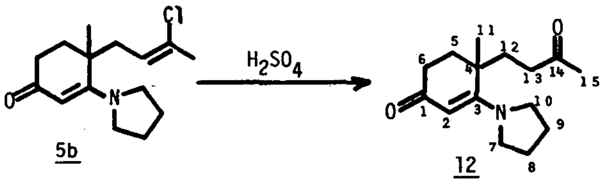
ir(CH_2Cl) 1680, 1600 cm^{-1}, bp$_{0.1}$220°C (67%), $\delta^{TMS}_{CDCl_3}$ = 6.72(m, 3H, A_RH's), 5.47 (t, broad, J_{cps}= 7,1H, C_9H), 4.52(s, 1H, C_2H), 3.80, 3.79 & 3.60 (s,s,s 9H, C_{12}, C_{15} & C_{16} H's), 3.50-2.20 (complex, 11H), 2.12 (s, broad, 3H, C_{11}H's)



ir(CH_2Cl_2) 2205, 1570 cm^{-1} bp$_{0.1}$ 200°C (55%) $\delta^{TMS}_{CDCl_3}$ = 6.66 (m,3H,ArH's), 5.90 (s,2H,C_{11}H's) 5.60(t, broad, J_{cps} =~7,1H, C_6H), 3.15 & 2.70 (s,6H,C_9 & C_{10}H's), 2.11 (s, broad, 3H, C_8H's)

The γ-alkylation of enaminoketones 1, 4, and 6, ester 8, and nitrile 10 is best accomplished through use of lithium diisopropylamide as the carbanion generating species rather than n-butyllithium.[2] In our hands, even at -78°C n-butyllithium catalyzed reactions are contaminated with varying amounts of carbonyl addition products that are not found when lithium diisopropylamide is used.

It is also interesting to note that hydrolysis of 5b with conc. H_2SO_4 converts the vinylchloride to a methyl ketone [12, 80%; λ^{EtOH}_{max} 305 nm; ir ($CHCl_3$) 1705, 1600, 1550 cm^{-1}; $\delta^{TMS}_{CDCl_3}$ = 4.91 (s, 1H, C_2H), 3.33 (broad, 4H, $-CH_2-N-CH_2-$), 2.59 (t, 4H, J = 6 Hz, C_6 H's, C_{13} H's), 1.50 - 2.31 (m, 11H, C_5H, C_8H, C_9H, C_{12}H, C_{15}H's), 1.1 (s, 3H, C_{11}H's), m/e = 235] while leaving the enaminoketone functional group intact. Experimental details of this work and results of our current studies on conjugated enamines are forthcoming.



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References

1. E. Wenkert, B. Channey, K. G. Dave, A. R. Jeffcoat, F. M. Schell, and H. P. Schenk, J. Amer. Chem. Soc., 95, 8427 (1973). A. I. Meyers and J. C. Sircar, Tetrahedron, 23, 785 (1967).
2. M. Yoshimoto, N. Ishida, and T. Hiraoka, Tetrahedron Lett., 39 (1973).
3. All compounds were analyzed by ir, nmr (pmr and cmr), u.v. and mass spectra; Purified by TLC or column chromatography on silica gel or alumina.
4. For different synthesis of compounds similar to 7 see: N. Heda, T. Tokuyama, and T. Sakan, Bull. Chem. Soc. Japan, 39, 2012 (1966).
5. For examples of intramolecular alkylations of α,β-unsat ketones and β-alkoxy-α,β-unsaturated ketones see: R. L. Cargill, T. E. Jackson, J. Org. Chem., 38, 2125 (1973). G. Stork and R. Danheiser, J. Org. Chem., 38, 1775 (1973).
6. Isolated in 35% yield after several TLC-separations to prepare an analytical sample. The actual yield of this alkylation product is considerably higher.
7. Reference 2 reports the γ-alkylation of simple enaminoesters and ketones. This is to our knowledge the first report of the γ-alkylation of enaminonitriles.
8. The synthesis and further reactions of 8 and 10 will soon be published.