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Cycloaromatization of α-Oxoketene Dithioacetals with Enaminone Derived Carbanions

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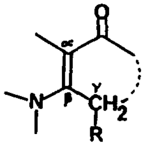
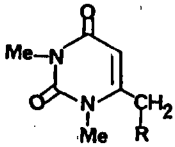
Abstract: Lithium enolates 3b and 6b derived from 1,3,6-trimethyluracil (3a) and 3-pyrrolidinocrotonate (6a) undergo regioselective γ-1,4- and γ-1,2-additions respectively with α-oxoketene dithioacetals 7 to yield the corresponding quinazolines and amino substituted aromatic compounds after subsequent cycloaromatization.

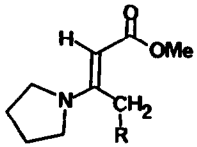
Cyclic and acyclic enaminones of the general formula 1 display multicentred nucleophilic reactivity (N-,O-,C-α) with various electrophiles.[1,2] Also the ß-methyl/methylene protons can be abstracted by LDA to afford the corresponding lithiated carbanions 2 in high yields.[2a,3] These anions have exhibited exclusive γ-regioselectivity towards alkylation and nucleophilic additions to carbonyl compounds.[2a,3] However their reactivity towards ambident electrophiles appears to have not been examined. Among others, the α-oxoketene dithioacetals constitute an excellent group of ambident 1,3-electrophilic components which on reaction with 2 could provide either a γ-1,2-and/ or γ-1,4-adducts. Both the adducts are important precursors for subsequent cycloaromatization. Our interest in the synthetic utility of α-oxoketene dithioacetals 7[4] prompted us to examine the reactivity of 7 with 3b and 6b as representative examples of cyclic and open-chain enaminones respectively. The reaction of 3b with 7 and the subsequent cyclization of the adduct constitutes a new general method for the synthesis of quinazolines 9[5] (Scheme 1), while the reaction of 6b with 7 under identical conditions could afford the corresponding substituted and condensed aniline derivatives 15 (Scheme 2). We herein report our preliminary results in this communication.



1 , R = H
2 , R = Li

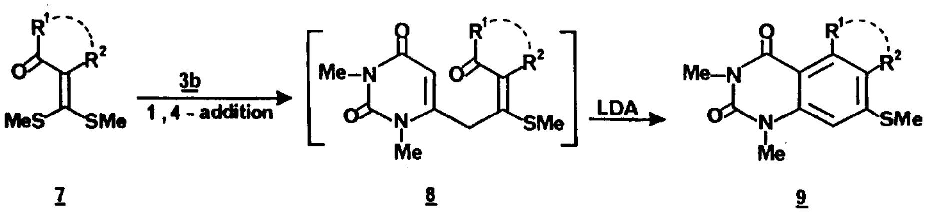


3a , R = H ; 3b , R = Li
4 , R = Me
5 , R = C_6H_5CHOH



6a , R = H
b , R = Li

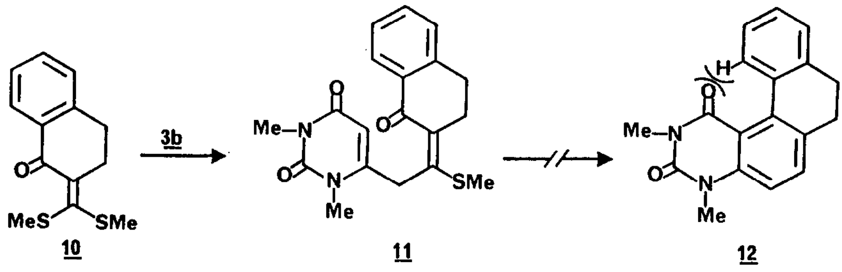
The anion 3b was generated by addition of 1,3,6-trimethyluracil (3a) to an equimolar amount of lithium diisopropylamide in THF at -40°C as white suspension which on treatment with methyl iodide afforded 1,3-dimethyl-6-ethyluracil 4 in 70% yield (m.p. 46-47°C). The site of methylation was unambiguously established by examining the ^{1}H nmr spectrum (CCl_4) of 4 : δ1.24 (t, 3H, CH_3); 2.52 (q, 2H, CH_2); 3.21 (s, 3H, N-CH_3); 3.40 (s, 3H, N-CH_3); 5.45 (s, 1H, H-5). No trace of 5- methylated product was formed in the reaction. Treatment of 3b with benzaldehyde similarly afforded the carbinol 5[6] in 65% yield. Thus the anion 3b behaves in similar fashion like its acyclic analog 6b yielding exclusively γ-alkylation products.[2a,2b,3a]



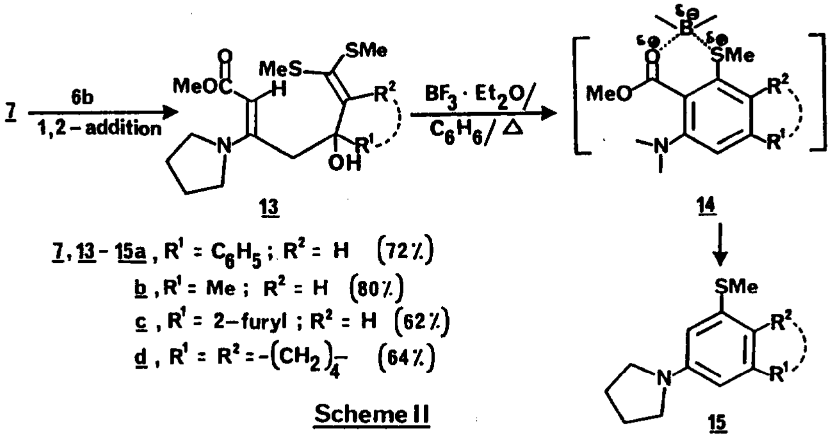
7-9a, $R^1 = C_6H_5$; $R^2 = H$ (86%)
b, $R^1 = Me$; $R^2 = H$ (73%)
c, R^1 = 2-furyl ; $R^2 = H$ (75%)
d, $R^1 = R^2 = -(CH_2)_4-$ (82%)

Scheme I

The anion 3b was next reacted with α-oxoketene dithioacetal 7a and the reaction mixture was stirred at -40°C for 45 min followed by overnight stirring at room temperature. The red coloured reaction mixture on work-up yielded a white solid (86%) characterized as 6-methylthio-8-phenylquinazoline derivative 9a on the basis of spectral and analytical data.[6] The quinazoline 9a is evidently formed by conjugate 1,4-addition of 3b to 7a and subsequent aromatization sequence. This reaction pathway was further confirmed by trapping the acyclic intermediate 8a through curtailing the reaction time (15 min).[6] The corresponding 8-methyl (9b), 8-(2-furyl) (9c) quinazolines and 7,8-tetramethylenequinazoline 9d were similarly obtained from the respective ketene dithioacetals 7b-d in 73-82% overall yields.[6] The reaction of 3b with oxoketene dithioacetal 10 from α-tetralone however gave only open-chain adduct 11 which could not be cyclized to 12 under varying conditions. Apparently, the steric crowding between *peri* substituents is responsible for failure of cycloaromatization.



The regiochemistry of addition of γ-lithioaminocrotonate 6b with α- oxoketene dithioacetals was however found to be different from 3b. Thus the reaction of 6b (generated by treatment of 6a with lithium diisopropylamide in THF containing tetramethylethylenediamine at -110°C) with 7a and subsequent work-up afforded only the unstable carbinol 13a through 1,2-addition and no trace of 1,4-adduct or the corresponding cycloaromatized product was isolated from the reaction mixture. The carbinol 13a underwent facile cycloaromatization (accompanied with simultaneous decarbomethoxylation) in the presence of boron trifluoride etherate in refluxing benzene to afford 3-(methylthio)-5-(N-pyrrolidino)biphenyl (15a), in 72% yield.[6] The corresponding toluene (15b), (2-furyl)- (15c)[6] and the tetrahydronaphthalene (15d)[6] derivatives were similarly obtained from the respective ketene dithioacetals 7b-d in good yields (62-80%) under identical conditions. Further work to probe into the regioselectivity of these reactions and their synthetic utility is in progress.



7,13-15a, $R^1 = C_6H_5$; $R^2 = H$ (72%)
b, $R^1 = Me$; $R^2 = H$ (80%)
c, $R^1 = 2\text{-furyl}$; $R^2 = H$ (62%)
d, $R^1 = R^2 = -(CH_2)_4-$ (64%)

Scheme II

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5. Lithium enolate anion derived from 5-carbonyl substituted 1,3,6-trimethyluracil is shown to react with electron deficient dienophiles to afford quinazolines in regio- and stereoselective manner: Senda, S.; Asao, T.; Sugiyama, I.; Hirota, K. *Tetrahedron Lett*. **1980**, 21, 531.
6. All the unknown compounds were characterised on the basis of spectral and analytical data. Spectral data for 8a: colourless crystals ($CHCl_3$/hexane); m.p.72°C. IR(KBr) : 1240, 1275, 1375,

1460,1560,1678 cm^{-1}. ^{1}H NMR (CDCl$_3$) : δ 2.53 (s, 3H, SCH$_3$); 3.36 (s, 3H, NCH$_3$); 3.53 (s, 3H, NCH$_3$); 4.21 (s, 2H, CH$_2$); 5.70 (s, 1H, H-5); 6.87 (s, 1H, =CH); 7.5-7.8(m, 3H, ArH); 7.9-8.2(m, 2H, ArH).

9a: Colourless crystals (CHCl$_3$/hexane); m.p. 154-155°C.IR(KBr) .: 1693, 1660, 1572, 1502, 1434, 1370, 1188 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.50 (s, 3H, SCH$_3$); 3.32 (s, 3H, NCH$_3$); 3.65 (s, 3H, NCH$_3$); 6.90 (d, 1H, J=1.5Hz, H-7); 7.05 (d,1H, J=1.5Hz, H-5); 7.18-7.52(m, 5H, ArH). MS:m/z 312 (M$^+$, 40%), 311 (45%).

9b: Colourless crystals (CHCl$_3$/hexane); m.p. 163-164°C.IR (KBr) : 1695, 1665, 1588, 1500, 1487, 1370, 1355, 1098 cm $^{-1}$. ^{1}H NMR (CDCl$_3$) : δ 2.50 (s, 3H, SCH$_3$); 2.70 (s, 3H, CH$_3$); 3.36 (s, 3H, NCH$_3$); 3.50 (s, 3H, NCH$_3$); 6.75 (d, 2H, J=2 Hz, ArH).

9c: Colourless crystals (CHCl$_3$/hexane); m.p. 193-194°C.IR (KBr) : 1700, 1662, 1586, 1485, 1426, 1368, 1286, 1102 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.55 (s, 3H, SCH$_3$); 3.34 (s, 3H, NCH$_3$); 3.60 (s, 3H, NCH$_3$); 6.55 (brs, 2H, furyl); 7.0 (d, 1H, J=1.5 Hz, ArH); 7.12 (d, 1H, J=1.5 Hz, ArH); 7.60 (brs, 1H, furyl).

9d: Colourless cyrstals (CHCl$_3$/hexane); m.p. 183-184^{b}C.IR (KBr): 1697, 1633, 1588,, 1488, 1420, 1353, 1295 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.58-1.95 (m, 4H, CH$_2$); 2.53 (s, 3H, SCH$_3$); 2.40-2.75 (m, 4H, CH$_2$); 3.42 (s, 3H, NCH$_3$); 3.61 (s, 3H, NCH$_3$); 6.68 (s, 1H, ArH). MS:m/z 290 (M$^+$,51%), 275 (34%).

11: Colourless crystals (CHCl$_3$/hexane); m.p. 190-191°C.IR(KBr): 1695, 1655, 1525, 1455, 1290, 1235 cm^{-1}. ^{1}H NMR (CDCl$_3$) : δ 2.27 (s, 3H, SCH$_3$); 2.65-3.00 (m, 4H, CH$_2$); 3.25 (s, 3H, NCH$_3$);3.46 (s, 3H, NCH$_3$); 4.13 (brs, 2H, CH$_2$); 5.5 (brs, 1H, C=CH); 7.0-7.32 (m, 3H, ArH); 7.68-7.90 (m, 1H, ArH).

15a: Colourless crystals (CHCl$_3$/hexane); m.p. 95-96°C.IR(KBr) : 1597, 1570, 1472, 1435, 1009 cm^{-1}. ^{1}H NMR (CDCl$_3$) : δ 1.85-2.10 (m, 4H, CH$_2$); 2.4 (s, 3H, SCH$_3$); 3.15-3.41 (m, 4H, NCH$_2$); 6.30 (brs, 1H, ArH); 6.37 (brs, 1H, ArH); 6.67 (brs, 1H, ArH); 7.15-7.58 (m, 5H, ArH). MS: m/z 269 (M$^+$, 60%), 268 (29%).

15b: Viscous liquid. IR (neat) : 3010, 1655, 1589, 1562, 1430, 1225 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.65-1.95 (m, 4H, CH$_2$); 2.12 (s, 3H, CH$_3$);2.39 (s, 3H, SCH$_3$); 2.95-3.26 (m, 4H, NCH$_2$); 6.05 (brs, 1H, ArH); 6.18 (brs, 1H, ArH); 6.3 (brs, 1H, ArH). MS : m/z 207 (M$^+$, 53%), 205 (40%).

15c: Viscous liquid. IR(neat) : 2850, 1580, 1460, 1360, 1260 cm^{-1}. ^{1}H NMR (CCl$_4$) : δ 1.73-2.0 (m, 4H, CH$_2$); 2.37 (s, 3H, SCH$_3$); 3.06-3.35 (m, 4H, NCH$_2$); 6.16 (brs, 1H, ArH); 6.30 (d, 1H, J=1.5Hz, ArH); 6.45 (s, 1H, furyl); 6.48 (brs, 1H, furyl); 6.78 (brs, 1H, ArH); 7.36 (brs, 1H, furyl).

15d: Pale yellow crystals (CHCl$_3$/hexane) ; m.p. 93-94°C.IR (KBr): 3015, 2945, 1644, 1522, 1418, 1195 cm^{-1}. ^{1}H NMR (CDCl$_3$) : δ 1.51-2.04 (m, 8H, -CH$_2$-); 2.35 (s, 3H, SCH$_3$); 2.45-2.78 (m, 4H, CH$_2$); 3.03-3.35 (m, 4H, NCH$_2$); 6.08 (brs, 1H, ArH); 6.19 (brs, 1H, ArH). MS : m/z 247 (M$^+$, 60%), 239 (20%).

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