Tetrahedron Letters,Vol.30,No.13,pp 1705-1708,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

REGIOSELECTIVE ALKYLATION OF DIANIONS OF CYCLIC 1.3-DIKETONES VIA THEIR MONO-DIMETHYLHYDRAZONES. SYNTHESIS OF C-4 SUBSTITUTED CYCLIC 1,3- DIKETONES

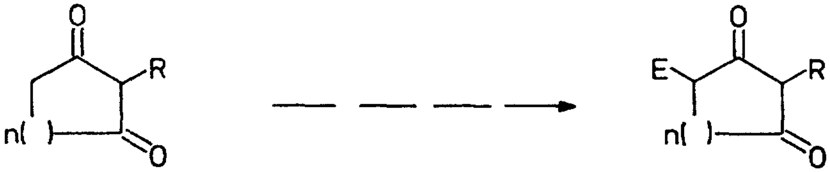
Ayhan S.Demir* [a] and Dieter Enders [b]

[a] Middle East Technical University, Department of Chemistry
06531-ANKARA ,TURKEY

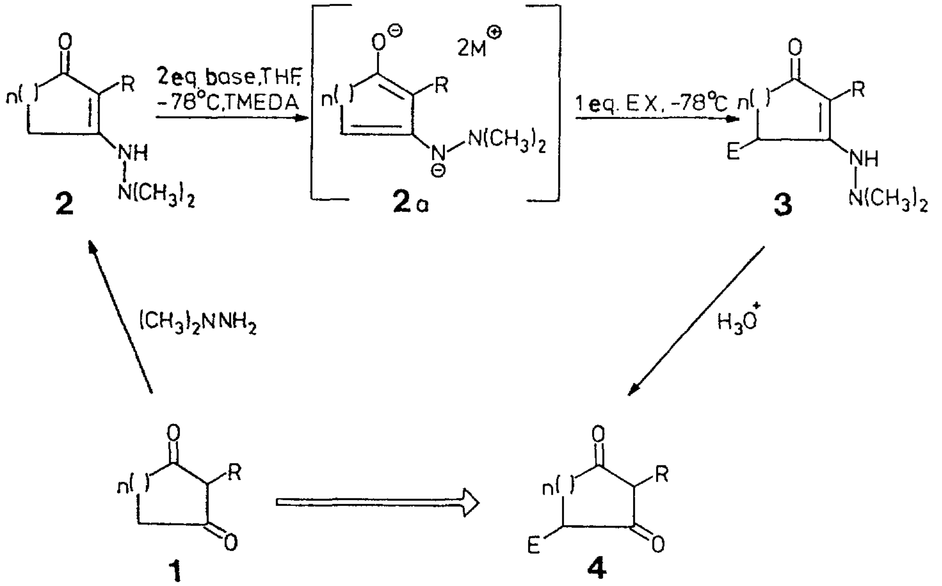
[b] Institut für Organische Chemie, Rheinisch-Westfaelische
Tecnische Hochschule, Professor-Pirlet - Str. 1,5100 Aachen,
FRG

Summary: Cyclic 1.3-diketones are transformed into the corresponding mono-dimethylhydrazones, which can be alkylated regioselectively at C-4 via dianions with various alkyl halides.

In view of the great importance of cyclic 1.3-diketones as starting materials in natural product synthesis, there is still a need for new generally applicable, regio-and stereoselective methods to functionalize these compounds.Cyclic 1.3-diketones, their enamines and enolethers are valuable intermediates in the construction of specifically substituted derivatives. Alkylation of the kinetic lithium enolates of enol ethers of symmetrical cyclic 1.3-diketones gave the C-6 substituted derivatives in high yields1-3).In constrast the alkylation and aldol condensation of lithium enolates of enaminoketones takes place at C-44-10). In this work, a versatile preparation of C-4 substituted cyclic 1.3-diketones via their dimetalated mono-dimethylhydrazones11) (mono-alkylation of dianions) has been investigated.



As is depicted in the scheme, cyclic 1.3-diketones <u>1</u> are transformed into their corresponding dimethylhydrazones[12,13], which according to the spectroscopic data (ir, nmr) exist as their tautomeric enehydrazinones <u>2</u>. Dimetalation with bases, such as n-BuLi or KDA in THF in the presence of TMEDA (1-4 equ.) at - 78°C[14], followed by treatment with various alkyl halides (1 equivalent) at-78°C yields after quenching with saturated ammonium-chloride solution at-78°C and purification by column chromatography (silica gel, ethylacetate-hexane 1:1) the C-4 substituted products <u>3a-h</u> in 56-65 % yield.



Scheme

As shown in the scheme, the double metalation reactions presumably involve the regioselective trapping of the azaenolate 2a at the position 4 and then protanation at position 2 (for instance, ^1H nmr spectrum of <u>3d</u> showed a doublet at δ 1.38 for the methyl protons, a singlet at δ 5.10 for the vinyl proton and a singlet at δ6.20 for the N-H proton).

After hydrolysis of the enehydrazinones <u>3a-h</u> with 6N HCl in methylene chloride (refluxing for 2h, during which time the reaction was monitored by TLC) yields the C-4 substituted cyclic 1.3-diketones <u>4a-h</u> in 59-65% yield(Table).

Table: C-4 substituted hydrazones 3 and diketones 4 .

n	R	E	hydrazones	yield %	ketones[15)]	Yield %
1	H	CH_3	3a	57	4a	59
1	CH_3	CH_3	3b	56	4b	61
1	H	C_2H_5	3c	59	4c	58
2	H	CH_3	3d	62	4d	60
2	H	C_2H_5	3e	61	4e	63
2	CH_3	CH_3	3f	65	4f	65
2	CH_3	$CH_2C_6H_5$	3g	57	4g	63
2[a)]	H	CH_3	3h	59	4h	61

[a)] 5,5-Dimethyl-cyclohexane-1.3-dione (dimedone) was used as starting material,

The spectroscopic data (ir, nmr, ms) and elemntary analyses of all new componds are in agreement with the structures given.

In conclusion, the efficient and overall highly regioselective alkylation of cyclic 1.3-diketones 1 to 4-substituted derivatives 4 described here, offers a new entry to these compounds, which are important starting materials in natural product synthesis.

Acknowledgements: We thank the chemical industry (Degussa AG, BASF AG,Bayer AG and Hoechst AG) for providing us with chemicals.

REFERENCES AND NOTES

1. G.Stork, R.L.Danheiser, J.Org.Chem. 38, 1775 (1973).
2. G.Stork, R.l.Danheiser, B.Ganem, J.Amer.Chem.Soc. 95, 3415 (1973).
3. N.M.Berry, M.C.P.Darey, L.M.Harwood, Synthesis 1986, 476.
4. M.Yoshimoto, N.Ishida, T.Hiraoka, Tetrahedron Lett. 1973, 39.
5. Y.L.Chen, P.S.Mariano, G.M.Litle, D.O.Brien, P.L.Huesmann, J.Org.Chem 46, 4643 (1981)
6. J.E.Telschow, W.Reusch, J.Org.Chem. 40 , 862 (1975).

7. T.A.Bryson, R.B.Gammill, Tetrahedron Lett. 1974, 3963.
8. R.B.Gammil, T.A.Bryson, Synthesis 1976, 401.
9. M.Mellor, G.Pattenden, Synth. Commun. 9, 1 (1979).
10. J.R.Hargreaves, P.W.Hickmott, B.J.Hopkins, J.Chem.Soc. (C) 1968, 2599.
11. For the dimethylhydrazone method (Corey-Enders method) see:
    a. E.J.Corey, D.Enders, Tetrahedron Lett. 1976,311.
    b. E.J.Corey, D.Enders, Chem.Ber., 111,1337 (1978).
    c. E.J.Corey, D.Enders, Chem.Ber., 111,1362 (1978).
12. For metalated chiral hydrazones of cyclic 1.3-diketones see:
    a. D.Enders, A.S.Demir, S.Franken, H.Puff, Tetrahedron Lett. 28 3795 (1987).
    b. N.N.Domnin, N.S.Gelbovskaya, Zh.Obshch. Khim 27, 665 (1957) (Chem. Abstr. 51, 16314h (1957)).
    c. U.Wolf, W.Sucrow, H.J.Vetter, Z.Naturforsch, 34b, 102 (1979).
13. a. A.S.Demir, diploma work, University of Bonn, 1982.
    b. A.S.Demir, dissertation, University of Bonn, 1985.
    c. For a recent application of chiral metalated hydrazones see: D.Enders, A.S.Demir,B.E.M.Rendenbach, Chem.Ber. 120, 1731 (1987).
14. For regioselective deprotonation sequence of 1.3-diketone Dimethylhydrazones, see D.Enders, A.S.Demir,P.Weuster, Kagaku-Zokan (Kyoto) 99,95 (1983).
15. The spectroscopic data of the ketones 4 are in agreement with those given in the literature:
    a. C.Gilling, J.Chem.Soc. 1913, 2033
    b. W.I.O.Sullivan, C .R.Hauser, J.Org.Chem. 25, 839 (1960)
    c. M.Vandewalle, F.Compernolle, Bull.Soc.Chim.Belges 75, 349 (1966)
    d. M.Vandewalle, Van Mijnsberghe, Bull. Soc.Chim Belges 79, 699 (1970)
    e. M.Vandewalle, N.Shamp, H.De Wilde, Bull.Soc.Chim.Belges 76,111 (1967)
    f. R.H.Brandbury, T.L.Gilchrist, C.W.Rees, J.Chem.Soc. Perkin I 1981, 3234
    g. E.Cant,M.Vandewalle, Organic Mass Spectrometry, 1971, 5, 1209.

(Received in UK 22 September 1988)