This article was downloaded by: [New York University]
On: 17 February 2015, At: 04:18
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of -5,6 Dihydro-1,4,2 Dioxazines from Hydroximates

A. Bel Hadj Amor [a], H. Mrabet [a] & B. Baccar [a]
[a] Labo. of Organic Synthesis Faculty of Sciences of TUNIS , 1060, TUNIS, TUNISIE
Published online: 23 Sep 2006.

To cite this article: A. Bel Hadj Amor , H. Mrabet & B. Baccar (1992) Synthesis of -5,6 Dihydro-1,4,2 Dioxazines from Hydroximates, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:14, 1985-1992, DOI: 10.1080/00397919208021331

To link to this article: http://dx.doi.org/10.1080/00397919208021331

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or

indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Downloaded by [New York University] at 04:18 17 February 2015

SYNTHETIC COMMUNICATIONS, 22(14), 1985-1992 (1992)

SYNTHESIS OF -5,6 DIHYDRO -1,4,2 DIOXAZINES FROM HYDROXIMATES

A. Bel Hadj Amor, H. Mrabet and B. Baccar

Labo. of Organic Synthesis Faculty of Sciences of TUNIS
1060 TUNIS - TUNISIE

Downloaded by [New York University] at 04:18 17 February 2015

ABSTRACT : Successive action of α-bromoesters and organometallics on hydroximates constitute a good way to obtain - 5,6 dihydro-1,4,2 dioxazines.

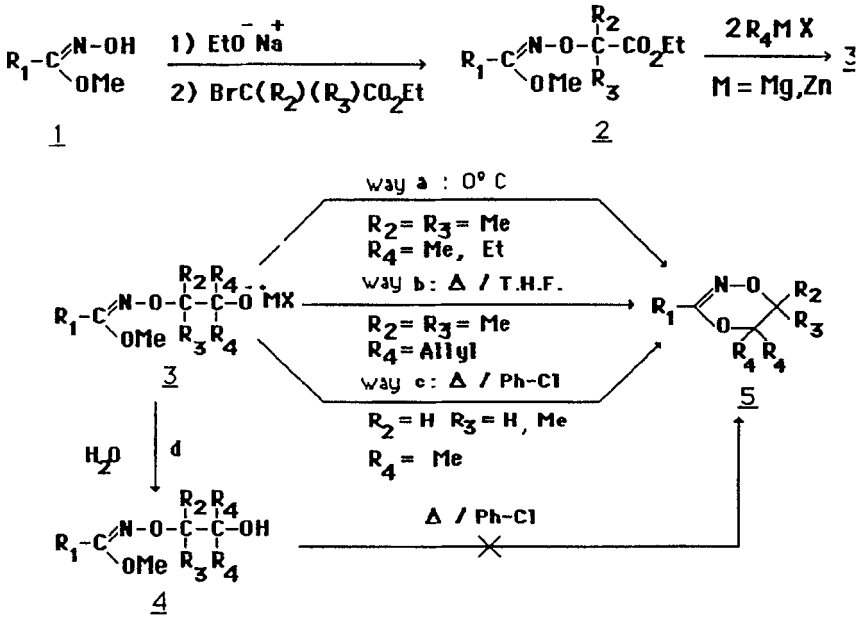
1. INTRODUCTION :

Despite extraordinary development made in heterocyclic chemistry , the - 1,4,2 dioxazines and their derivatives were not well known . Some works were published and they concerned dihydro[1-6] and tetrahydro-1,4,2 dioxazines [7,8,9]. In this work we show that hydroximates constitute good substrates for these heterocyclic derivatives .

2. RESULTS AND DISCUSSION :

The passage from hydroximates 1 to -5,6 dihydro-1,4,2 dioxazines 5 is realizable in three steps . The action of α-bromoesters on hydroximate salts gives hydroximate- esters 2 . Treated by organometallics these compounds are transformed into salts of hydroximate-alcohols 3 which can be cyclized to give -5,6 dihydro-1,4,2 dioxazines 5 (scheme :1)

Copyright © 1992 by Marcel Dekker, Inc.



Scheme : 1

2-1. Preparation of hydroximate-esters : 2

O- alkylation of the =N-OH group in presence of alcoholates is well known[1,10-13]. In the same conditions α-bromoesters react with 1 and lead to hydroximate - esters 2 with good yield : 2a : R_1= Ph , R_2 = R_3 =H ; 2b, : R_1 =Ph , R_2 = R_3 = Me; 2c : R_1 = $PhCH_2$, R_2 =H , R_3 = Me ; 2d : R_1 = $PhCH_2$, R_2 = R_3 = Me .

Compounds 2 are liquid and can be purified by distillation under low pressure . They are easily identified by IR and ^1H NMR spectroscopy. This last technique shows that they are obtained in a mixture of two isomers Z and E (splitting of methoxy signal).

Downloaded by [New York University] at 04:18 17 February 2015

Downloaded by [New York University] at 04:18 17 February 2015

2.2. Preparation of hydroximate - alcohol salts 3 and Their corresponding alcohols 4 :

It is demonstrated that compounds containing carboxylic esters (-CO_2R) and imidic group (-C(OR)=N-) react with organometallic carbanions only by the first function[14] .This selectivity is independent of reagent quantity. In the presence of two equivalents or more of Grignard reagent (RMgX or RZnX) hydroximate-esters 2 are transformed in alcoholates 3 which are ringclosed at room temperature or by heating in various solvents and give-5,6 dihydro-1,4,2 dioxazines 5 Those which do not lead to heterocyclic derivatives 5 at room temperature give hydroximate-alcohols after hydrolysis (scheme 1 way d) .Three compounds of type 4 are isolated , purified by distillation and identified by IR and ^1H NMR spectroscopy . 4a : R_1 = Ph , $R_2 = R_3$ = H , R_4 = Me ; 4b : $R_1 = PhCH_2$, $R_2 = R_3$ = Me , R_4= CH_2-CH=CH_2 ; 4c : $R_1 = PhCH_2$, R_2 = H , $R_3 = R_4$ = Me

2.3. Preparation of -5,6 dihydro-1,4,2 dioxazines 5 :

According to the nature of the substitutes, the passage from alcoholates 3 to - 5,6 dihydro-1,4,2 dioxazines 5 may be done at room temperature (scheme 1,way a R_2=R_3=Me and R_4=Me,Et) or by heating reagents in solvents : (THF , way b , when R_2 = R_3 = Me and R_4 = CH_2-CH=CH_2 or Phenylchloride , way c , when R_2= H , R_3= H , Me and R_4=Me). In total, six -5,6 dihydro-1,4,2 dioxazines are obtained . They are identified by IR and ^1H NMR spectroscopy and for some of them by elemental analysis .

	R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4
5a	Ph	Me	Me	Me	5d	Ph	Me	Me	allyl
5b	$PhCH_2$	Me	Me	Me	5e	Ph	H	H	Me
5c	$PhCH_2$	Me	Me	Et	5f	$PhCH_2$	H	Me	Me

On the other hand whatever may be the nature of alkyl groups R_2, R_3 and R_4, alcohols 4 cannot be converted in 5 even by heating for a long time in phenylchloride .

3. EXPERIMENTAL PART :

Uncorrected melting points were determined by capillary with a BUCHI apparatus.IR spectrums are registered with a Perkin - Elmer apparatus model 681 in solution of chloroform or in suspension in perfluoried hydrocarbon. NMR spectrums are registered with an apparatus Jeol C-HL 60 (60 MHz) in general in solution of $CDCl_3$ with TMS as internal reference. Chemical shifts are expressed in ppm. Elemental anlysis are made at the Microanalysis Center of the University Paul Sabatier TOULOUSE (FRANCE) . Synthetic methods of compounds 2 , 3 , 4 and 5 are similar for each serie. We describe one example of each .

3.1. Synthesis of hydroximate-esters 2

Compound 2a : In a three-neck funnel equiped by a cooler, a dropping funnel and a magnetic stirrer, we put, under nitrogen atmosphere 2,5 g (25 mmoles) of tBuOK and 20 ml of dry THF. Then we add on a drip a solution of 3,77g (25 mmoles) of Methyl benzohydroximate in 10 ml of THF at 0°C. After stirring for 1 hour we add 4,17g (25 mmoles) of Ethyl bromoacetate in 10 ml of THF in small quantities at the same temperature. Stirring is prolonged to 12 hours at room temperature followed by hydrolysis of the reactional mixture with a saturated solution of NH_4Cl. The organic phase is then separated while the aquous phase is extracted three times with 30 ml of diethylether. Organic parts are collected, dried and after removing the solvent, the residue is purified by distillation under vacuum :

2a Bp : 140/2 Yield : 58% IR(cm^{-1}) : $\nu_{C=N}$ = 1630 $\nu_{C=O}$ = 1760

^1H NMR ($CDCl_3$):7,9 to 7,16(m,5H) ; 4,51(s, 2H) ; 4,2(qt, 2H) ; 3,96 et 3,73(s splitted, 3H) and 1,2 (t, 3H).

Downloaded by [New York University] at 04:18 17 February 2015

Downloaded by [New York University] at 04:18 17 February 2015

2b bp : 120/1,4 Yield : 48% IR (cm^{-1}) : $\nu_{C=N}$ = 1630 $\nu_{C=O}$ = 1735

^1H NMR($CDCl_3$) : 7,86 to 7,1 (m,5H);4,13(qt, 2H) ; 4,00 and 3,66 (s splitted , 3H) 1,53 (s splitted , 6H) ; 1,23 (t splitted , 3H) .

2c bp : 132/2 yield : 45% IR (cm^{-1}) : $\nu_{C=N}$ = 1645 $\nu_{C=O}$ = 1745

^1H NMR ($CDCl_3$) 7,27 (s, 5H) ; 4,53 (qt, 1H);4,16(qt,2H);3,7(s splitted , 2H);3,53(s splitted , 3H)1,43(d,3H); 1,23(t,3H).

2d bp : 122/1,1 yield : 49% IR (cm-1) : $\nu_{C=N}$ = 1645 $\nu_{C=O}$ = 1735

^1H NMR ($CDCl_3$) : 7,23 (s, 5H); 4,16(qt, 2H) ; 3,73(s, 2H);3,56 (s splitted , 3H); 1,5 (s, 6H)1,2 (t, 3H).

3.2. Synthesis of hydroximate - alcohols 4 :

Compound 4a : To a solution of 100 mmoles of methyl magnesium iodate[17] in 20 ml of dry THF , is added dropwise at 0°C 3g (12,5 mmoles) of $PhC(OMe)=NOCH_2CO_2Et$ **2a** . The mixture is stirred for 12 hours at room temperature and then hydrolised using 50 ml of an aquous saturated solution of NH_4Cl and 50g of ice. After extraction by diethylether and drying extracted parts ., the solvent is removed and the hydroximate-alcohol is isolated by distillation under vacuum.

4a bp : 126/2 yield : 61% IR (cm^{-1}) : $\nu_{C=N}$ =1625 $\nu_{OH(ass)}$ = 3430 $\nu_{OH(free)}$ = 3600 ^1H NMR: ($CDCl_3$): 7,93 to 7,1 (m,5H), 3,83 (s splitted , 3H); 3,73 (s, 2H); 3,43 (ma, 1H); 1,2 (s, 6H)..

Elemental analysis : calc. : %C = 64,57 ; %H =7,62 ; % N = 6,,28

found : 64,38 7,68 6,20

4b* bp :152/2 yield : 40 % . IR (cm^{-1}): $\nu_{C=N}$ =1640 $\nu_{OH(ass)}$ = 3420 $\nu_{OH(free)}$ = 3600 ^1H NMR:($CDCl_3$): 7,16(s,5H); 6,33 to 5,33 (ma, 2H); 5,26 to 4,73 (ling, 4H); 4,2(qt,1H); 3,66(s, 2H); 3,43(s, 3H); 3,23(ma, 1H); 2,23(m, 4H); 1,33(d, 3H).

4c F:181°C yield : 52% IR (cm^{-1}) : $\nu_{C=N}$ =1640 $\nu_{OH(ass)}$ =3400 $\nu_{OH(free)}$ = 3600

(*Bromide allylzinc was used instead of iodate methylmagnesium).

3.3. Preparation of -1,4,2 dioxazines 5 :

These compounds were prepared by three methods.

Method a : We proceed similarly as in the preparation of compounds 4. After hydrolysis, extraction with diethylether, drying organic parts and removing solvent, the distillation of crude residue leads to dioxazines 5 .

5a $C_{13}H_{17}NO_2$ bp : 106/0,4 yield : 44% IR(cm^{-1}) : $\nu_{C=N}$ = 1660 ^1H NMR : ($CDCl_3$) ; 7,88 to 7,2 (m, 5H) ; 1,33 (s , splitted, 12H)

5b $C_{14}H_{19}NO_2$ bp : 112/1,5 yield: 54% IR (cm^{-1}): $\nu_{C=N}$ =1650 ^1H NMR : ($CDCl_3$) 7,5 to 7,2 (m,5H) ; 3,66 (s , splitted; 2H) ; 1,3 (s, splitted , 12 H).

Elemental analysis : calc. : %C = 72,1 ; %H = 8,15 ; % N = 6,00

found : 71,83 8,69 6,43

5c $C_{16}H_{23}NO_2$ bp : 118/0,7 yield : 35% IR (cm^{-1}) : $\nu_{C=N}$ = 1650 ^1H NMR:($CDCl_3$) :7,43 to 7,16 (m,5H) ; 3,66 (s , splitted , 2H) ; 2,2 to 1,2 (m, 4H) ; 1,2 (s , 6H) ; 0,9 (t , splitted , 6H).

Method b : A solution of 20 mmoles of $PhC(OMe)=NOC(Me)_2C(allyl)_2OZnBr$ in 50 ml of THF is heated at refluxing for 12 hours . The solvent is removed under atmospheric pressure and then the residue is distilled under vacuum.

5d $C_{17}H_{21}NO_2$ bp : 158/5 yield : 69% IR (cm^{-1}) : $\nu_{C=N}$ = 1640 ^1H NMR ($CDCl_3$) : 7,9 to 7,16 (m,5H) ; 5,93 (m , 2H) ; 5,07 (m,4H) ; 2,43(d,4H); 1,5(s,6H).

Downloaded by [New York University] at 04:18 17 February 2015

Method c : A solution of 10 mmoles of the hydroximate-alcohol salts 3a or 3c in 10 ml of phenylchloride is heated at refluxing temperature for 12 hours. After cooling the mixture and removing the solvent , a solid is isolated. It is then purified by recrystallisation in methanol.

5e $C_{11}H_{13}NO_2$ F=90 °C yield : 65% IR (cm^{-1}) : $\nu_{C=N}$ = 1650

^1H NMR:($CDCl_3$) : 7,8 to 7 (m, 5H) ; 2,95 (s, splitted, 2H) ; 0,9 (s, 6H).

Elemental analysis : calc. : %C = 69,1 ; %H = 6,80 ; % N = 7,32

found : 69,58 6,42 7,11

5f $C_{13}H_{17}NO_2$ F : 132 °C yield : 46% IR (cm^{-1}) : $\nu_{C=N}$ = 1650

^1H NMR :($CDCl_3$):7,5 to 7(m,5H); 3,5(qt 1H) 3,46(s,2H); 1,2(d,3H); 1,1(s, 6H).

The authors are indebted to Professor J. BARRANS of the University Paul Sabatier of TOULOUSE for his help and constructive suggestions .

REFERENCES :

(1) Johnson, J.E.; Springfield, J.R.; Mwang, J.S; Hayes L.J. Cunningham, W.C. and McClaugherty, D.L. : J. Org. Chem. 1971 36,2, 284

(2) Nakatsuji,Y.; Ikeda,I. and Okahara,M. : Nippon Kagaku Kaishi 1975 6 1041 ; C. A. 1975 83 206218 .

(3) Chieh,C. and Mackay D.: Acta Cryst.1979 B35 1835 .

(4) Mackay,D.; Daole,H. and Dust,J.M. : J. Chem. Soc. Perkin Trans. 1980 1 11 2408.

(5) Amlayky,N.;Leclerc, G. and Capy, A. : J. Org. Chem. 1982 47 577.

(6) Richard,G.; Knaus,E.E. and Dubey,S.K.: Acta Cryst.1985 C41 456.

(7) Jones, R. A.Y. ; Katritzky,A.R. ; Martin,A. and SABA S. : J. Chem Soc. Chem. commun. 1973 23 908.

(8) Riddel F.G., Berry,M.H. and Turner E.S.: Tetrahedron 1978 34 1415 .

Downloaded by [New York University] at 04:18 17 February 2015

(9) Fruchier, A.; Moragues,V. ; Petrus,C. and Petrus, F.: Bull. Soc. Chim. de France 1984 5 6 173 .

(10) Khomutov,R.M. ; Severin, E.S.; Gnuchev,N.V. and Derevanko,T.Ya. : Izv. Akad. Nauk. SSSR ser. khim. 1967 1820 C. A. 1968 68 39053.

(11) Markovo,Yu ; Ostrounova, N.G and Shchukina, M.N : Zh. Org. Khim. 1967 3 1207 .

(12) Eloy F. and Lenaers R. : Chem. Rev. 1962 155 .

(13) Brady, O.L. and Perkin , F.H . : J. Chim. Soc. 1930 226

(14) Bellassoued, M. ; Gaudemar, M.; Hajjem, B. and Baccar, B. : Bull. Soc. Chim. Belg. 1986 95 65.

(15) Pinner, A. : Ber. 1877 10 1889

(16) Schmidt, E. : Ber. 1914 47 3852 .

(17) Watson, S.C. and Eastham, J.F. : J. Organometal. Chem. 1967 9 165 .

(Received in USA 3 March, 1992)

Downloaded by [New York University] at 04:18 17 February 2015