Synthesis of new pyrazolenines and cyclopropenyl alcohols directly from propargyl alcohols

Naceur Hamdi[a]*, Pierre Henry Dixneuf[b], Youssef Arfaoui[c] and Ezzeddine Haloui[c]

[a]*Institut National de Recherche et d'Analyse Physico Chimique, Technopôle de Sidi Thabet 2020, Tunisie*

[b]*Institut de Chimie de Rennes, UMR 6509 CNRS - Université de Rennes, Campus de Beaulieu, 35042 Rennes, France*

[c]*Laboratoire de Chimie Physique, Départment de Chimie de la Falculté des Sciences de Tunis, 1060, Tunisie*

The 1,3-dipolar cycloaddition of 2-diazopropane **1** to propargylic alcohols is regioselective and leads to 3*H*-pyrazoles **3** in good yield. The surprising formation of the tetrasubstitued pyrazolenine **4c** from $HC{\equiv}CCH_2OH$ and **1** can be explained via the 1,3–dipolar cycloadduct intermediate followed by a second cycloaddition of **1** to the C=C double bond and loss of dinitrogen. The photolysis of the antibacterial pyrazolenines **3** and **4** selectively gives α and β dimethylcyclopropenyl alcohols **5** and **6**.

Keywords: diazoalkane, cycloaddition, photolysis, pyrazolenines, cyclopropenylalcohols

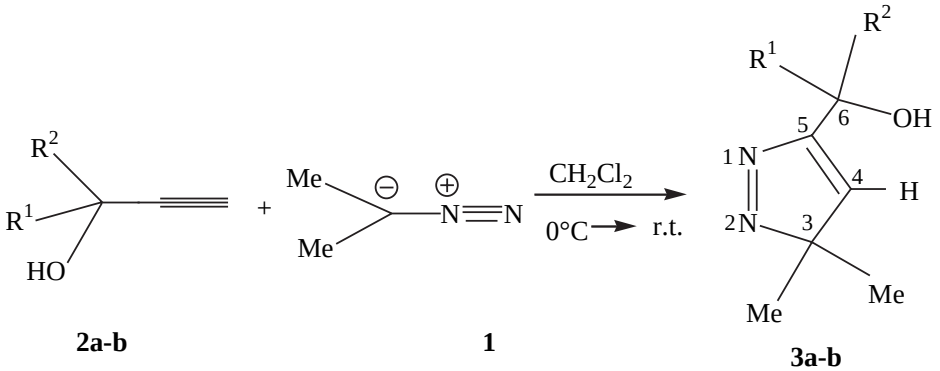
Three-membered strained ring systems constitute an attractive class of molecules as synthetic intermediates.[1-3] Among them the rigid, unsaturated cyclopropenes are the key to selective useful transformations[4,5] such as regioselective additions of organometallics[6-8] or cycloadditions.[9,10] Cyclopropene derivatives have also potential biological activity since their structural feature is included in valuable natural products such as phorbol and chrysanthemic acid.[11,12] An approach for the synthesis of cyclopropene derivatives is offered via the formation of cyclopropenyl lithium, generated from 1,1–dibromo-2-chlorocyclopropane.[13] The metal catalysed addition of carbene sources to alkynes constitutes the most direct access to cyclopropene derivatives[14] most of them involving rhodium[15,16] and copper[17] catalysts. However, the metal catalysed addition of diazoalkane is not always satisfactory with bulky and functional alkynes. The carbene easily inserts into heteroatom-hydrogen bonds[18] and the insertion of the triple bond into the metal─carbene bond is in competition with cyclopropenation.[19] When carbene insertion into heteroatom─hydrogen bond has to be prevented, the initial regioselective 1,3-dipolar addition of diazoalkane to functional alkynes, followed by photochemical elimination of dinitrogen, constitutes an alternative for the preparation of cyclopropenes with an α–functional group. Moreover, when the functional group of alkynes controls the regioselectivity of diazoalkane 1,3-cycloaddition, this approach allows the simple access to functional pyrazolenines with potential biological properties.[20]

We now report the synthesis of new antibacterial pyrazolenines by regioselective 1,3-dipolar cycloaddition of the versatile 2-diazopropane to non protected propargylalcohols, whereas the unsubstituted propargyl alcohol allows the double addition of 2-diazopropane and gives a pyrazolenine with formal insertion of the dimethylcarbene into a carbon─carbon bond. We also show that the photolysis of the 3*H*-pyrazoles leads to new alcohols containing the cyclopropenyl unit.

Results and discussion

Preparation and properties of pyrazolenines **3** *and* **4**: Whereas the $Rh_2(OAc)_4$ catalysed addition of diazoalkanes to propargyl alcohols readily gives the insertion of the carbene into their O-H bond, with only a small amount of cyclopropenation of the resulting propargylic ether,[18] the 2-diazopropane **1**, reacts at 0 °C with 1,1-diphenyl-2-propyn-1-ol **2a** in dichloromethane and exclusively gives, after 10 h of reaction, only one adduct **3a** isolated in 75 % yield and corresponding to a regioselective 1,3-dipolar cycloaddition (Scheme 1).

The structure of this compound **3a** was determined by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum shows singlets at 1.45 ppm for to the methyl protons, and at 4.17 ppm and 6.30 ppm for the hydroxylic and the ethylenic protons. The addition regioselectivity in **3a** formation was established by ^1H─^{13}C HMBC 2D- NMR that shows the C_5─C_4─C_3─Me linkages. The ethylenic proton correlates only with three carbon atoms C_6, C_5 and C_3. The methyl protons correlate with C_3 and with the ethylenic carbon C_4, consistent with the



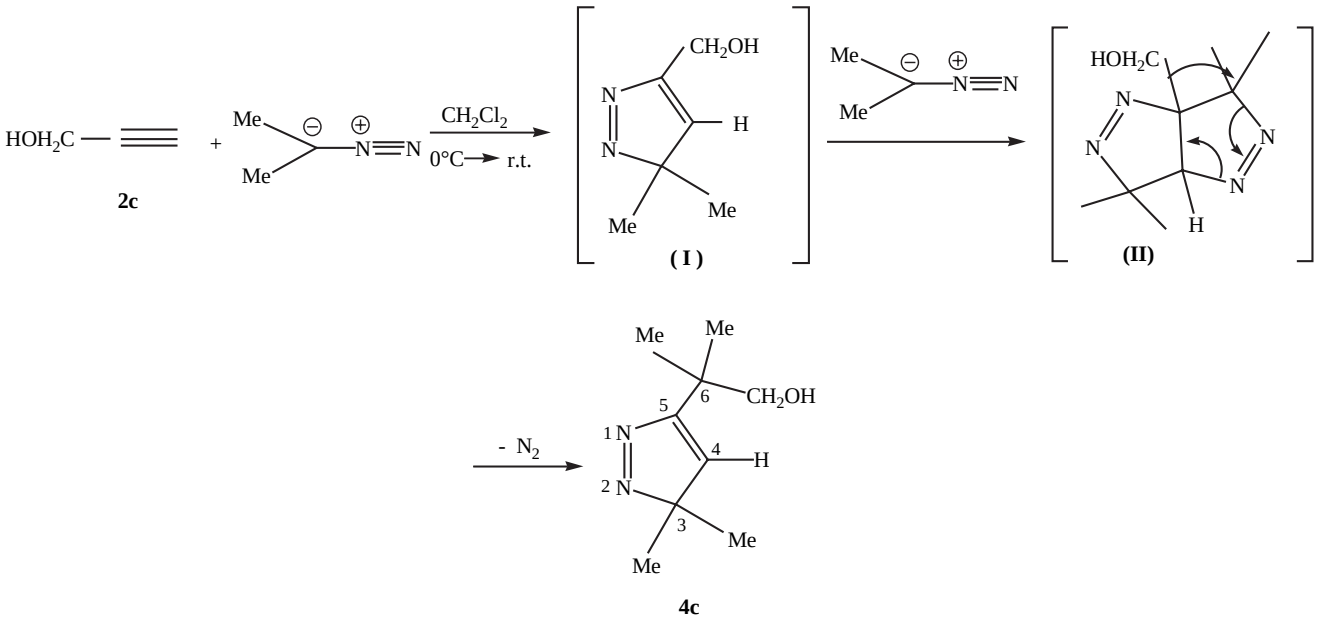
2a-b **1** **3a-b**

a : R^1, R^2 = Ph

b : R^1 = Ph , R^2 = Me

Scheme 1 Synthesis of pyrazolenines **3**.

* Correspondent. Email: hamdi_naceur@yahoo.fr



Scheme 2 Synthesis of the tetrasubstituted pyrazolenine **4**.

neighbouring C_3–C_4 connexion. The NOESY spectrum shows a nOe cross peak between the ethylenic and the aromatic protons. The cycloaddition regiochemistry leading to derivative **3a,** with the linkage of the nitrogen atom with the unsaturated carbon connected to the functional group, corresponds to that observed for the 1,3-dipolar cycloaddition reaction of simple diazoalkanes with α,β-unsaturated ketones [21]

Analogously the 1,3-dipolar cycloaddition reaction of 2-diazopropane with propargyl alcohol **2b**, performed at 0 °C in dichloromethane, was completed in less then 10 h and led to a monoadduct **3b** with the same regioselective addition mode of **1** to the triple bond (Scheme 1). The HMBC spectrum showed correlations between the ethylenic proton and the carbons C_3 and C_5 and between the methyl protons and the carbons C_3 and C_4.

By contrast the unsubstituted propargylic alcohol **2c** reacts with an excess of 2-diazopropane and was completely transformed after 10 h at 0 °C to surprisingly give the tetrasubstituted pyrazolenine **4c** isolated in 73 % yield (Scheme 2). The ^{1}H NMR spectra of **4c** showed the presence of three methyl groups: two equivalents (a,b) and two enantiotopic (c,d) groups and singlets at δ 4.01 ppm for the OH group, δ 4.86 ppm for the methylenic and δ 6.70 ppm for the ethylenic protons. The formation of **4c** which includes the incorporation of two CMe_2 groups arising from the diazoalkane can be explained via the formation of the expected cycloadduct intermediate (**I**), followed by a second cycloaddition of diazoalkane to the remaining double C=C bond to give the intermediate (**II**). The later is not stable at room temperature, loses dinitrogen and undergoes rearrangement of the carbon skeleton leading to **4c.**

The addition of an excess of the 2-diazopropane to the alkynes **2a–b** did not give the corresponding bisadduct of diazoalkane. It is likely that the bulkyness of the CR^1R^2OH group, close to the C=C bond in the intermediate (**I**), prevents the second addition of diazopropane, that is allowed by the smaller propargyl alcohol CH_2OH group.

The antibacterial activity of the obtained pyrazolenines **3a, b** and **4c** has been studied. They have been tested opposite a pathogenic bacterial stump and have shown antibacterial activity against the original *staphyloccocus aureus*. The pyrazolenine **3b** offers the strongest antibacterial activity.[22]

Photochemical transformation of the obtained pyrazolenines into cyclopropene derivatives

The photochemical study of 3*H*-pyrazoles has been attempted in the search for a route to cyclopropenyl tertiary alcohols. Irradiation of **3a** in dry dichloromethane at 300 nm and at room temperature for 0.5 h led to the exclusive formation of the *gem*-dimethylcyclopropene **5**. (Scheme 3). The formation of cyclopropene **5** arises from the loss of N_2 and cyclisation of the vinylcarbene intermediate (**III**).

The structure of **5** was determined via a detailed mono and bidimensional NMR study. In ^{13}C NMR a signal at 20.3 ppm corresponds to the methyl groups and the carbon nucleus $=C_2$-H carbon appeared at 142.3 ppm. The *gem*-dimethylcyclopropene structure of **5** was consistent with an analysis of the ^{1}H–^{13}C HMBC spectrum.

The analogous photochemical reaction (300 nm) of pyrazolenine **4c** in dichloromethane at room temperature led to cyclopropene derivative **6** possessing a β-hydroxy group isolated in 70% yield. (Scheme 4).

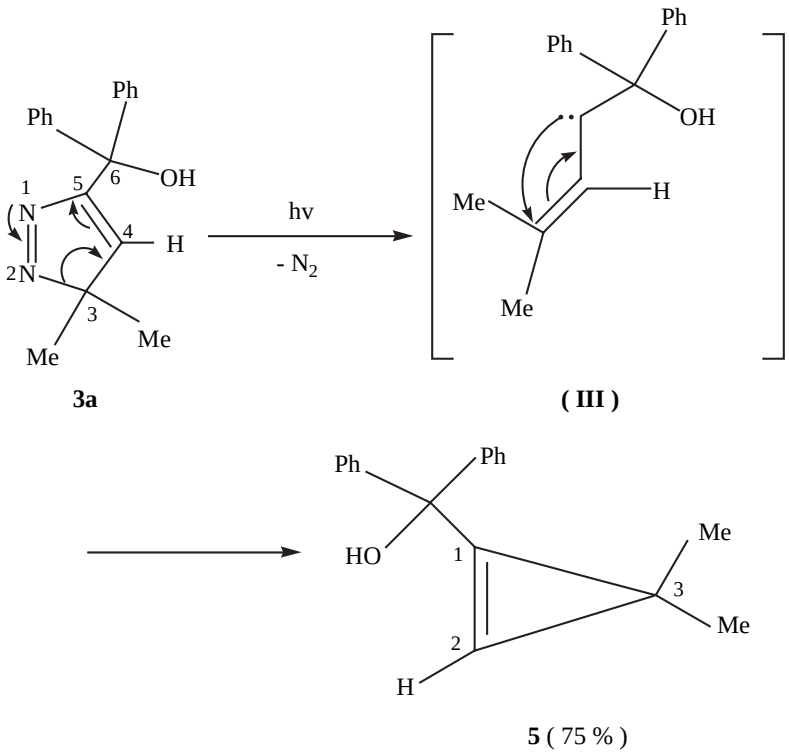
The above two consecutive transformations give a straightforward access, from propargyl alcohols, to cyclopropene derivatives with an α or β-hydroxy group directly. This simple method is complementary of the access to 3-hydroxymethylcyclopropenes, via $Rh_2(OAc)_4$ catalysed addition of diazoacetate to alkynes followed by reduction, a route restricted to the access of primary cyclopropenyl alcohols,[23] and is an alternative to the use of 1,1–dibromo-2-chlorocyclopropane via cyclopropenyl lithium.[13]

Conclusion

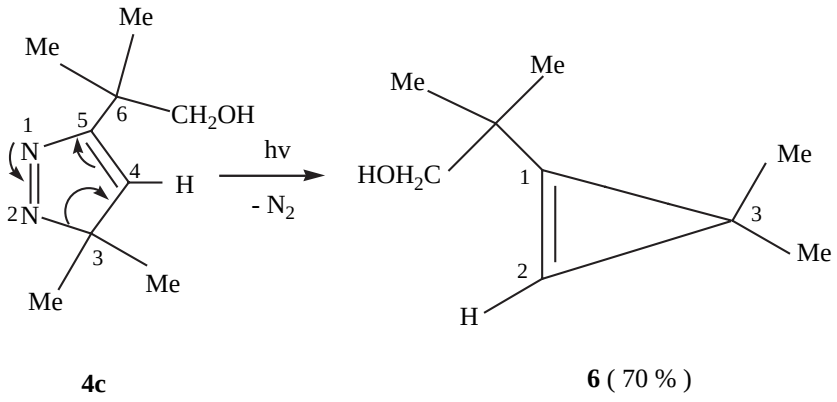
This study demonstrates that the regiochemistry of the addition of the 2-diazopropane with the triple bond of propargyl alcohols is completely controlled by the nature of the CR_2OH group and diazoalkane, and selectively affords new antibacterial 3*H*-pyrazoles. The photochemical reaction of these 3*H*-pyrazoles selectively leads to α- and β-hydroxy cyclopropenes. The overall transformation constitutes a simple straightforward route to substituted cyclopropenyl alcohols.

Experimental

NMR spectra were recorded at room temperature on a AC 300 MHz in $CDCl_3$. Chemical shifts are expressed in ppm downfield from



Scheme 3 Preparation of α-hydroxycyclopropene **5**.



Scheme 4 Preparation of β-hydroxycyclopropene **6**.

$SiMe_4$ (^1H and ^{13}C). The IR spectra were recorded on a Bruker FT-IR IFS 28 in the region between 4000 and 400 cm^{-1}, (KBr).

Mass spectra were obtained with a Hewlett- Packard 5880 A Spectrometer. In this case electron impact techniques were employed. Melting points were determined on a Buchi apparatus and were uncorrected. TLC was performed on aluminum–backed plates coated with silica gel 60 with F254 indicator. Column chromatography was carried out on a silica gel 60.

Cycloaddition reaction of 2-diazopropane with propargylalcohols **2a-c**. *Synthesis of pyrazolenines* **3a–b** *and* **4c:** To a stirred solution containing (1g) of alkynes **2a–c** in 40 ml of anhydrous dichloromethane at 0 °C were added, in small fractions, 10 ml of a 2.6 M etheral solution of 2-diazopropane freshly prepared at –60 °C. The reaction was followed by TLC (hexane-ethylacetate 1/1 as elutant) and the reaction was maintained till the alkynes **2a–c** had totally reacted. The solution was allowed to react for 10 hours at 0 °C and the solvent was evaporated under reduced pressure. The obtained pyrazolenine was purified according to the case by filtration on a column of silica or by recrystallisation in a mixture of dichloromethane–petroleum ether to afford **3a, b** and **4c** with the following characteristics:

3a: Yield: 75 %; m.p = 163°C; Anal. Calcd for $C_{18}H_{18}ON_2$ C:77,69%, H: 6,47%, N: 10,07%, O: 5,77%, found: C: 73,3%, H: 6,4%, N: 10,4%, O: 9,90%; ms: 261 ($(M^{+\cdot})$–OH, 41.5%); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (s, 6H, CH_3); 4.17 (s, 1H, OH), 6.35 (s, 1H, =C-H); 7.28–7.38 (m,10 H, H_{arom}).^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 20.3 (CH_3), 77.3 (C_6), 93.7 (C_3), 142.4 (C_5), 127.1–144.3 (C_{arom}), 160.4 (C_4). IR νcm^{-1} (KBr): ν_{OH} = 3293, $\nu_{C=C}$ = 1599.

3b: Yield: 75%; Anal. Calcd for $C_{13}H_{16}ON_2$ C:72,22% H: 7,40%, N: 12,96%, O: 7,41%, found: C: 72,1%, H: 7,2%, N: 12,8%, O: 7,3%; ms: 199 ($(M^{+\cdot})$-OH, 13.2 %). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39 (s, 6H, CH_3); 1.90 (s, 3H, CH_3); 3.93 (s, 1H, OH), 6.61 (s, 1H, =C–H); 7.24–7.33 (m,10H, H_{arom}). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 20.2 (CH_3), 29.2 (CH_3), 87.5 (C_6), 93.5 (C_3), 145.3 (C_5), 124.8–159.8 (C_{arom}), 161.4 (C_4). IR νcm^{-1}(KBr): ν_{OH} = 3397, $\nu_{C=C}$ = 1492.

4c: Yield: 73 %; Anal. Calcd for $C_9H_{16}ON_2$ C: 64,28% H: 9,52%, N: 16,66%, O: 9,53%, found: C: 64,1%, H: 9,4%, N: 16,5%, O: 9,4%; ms: 168 ([M]$^{+\cdot}$, 19,8%). ^1H NMR (300 MHz, $CDCl_3$) δ**:**1.30 (6H, s, Me(a,b)),1.80 (3H, s, Me (c)),1.90 (3H, s, Me (d)), 4.81(CH_2), 4.0 (1H, s,OH), 6.70 (1H, s,CH). ^{13}C NMR (75.47MHz, $CDCl_3$) δ: 20.4 ($CH_{3(a,b)}$),25.2($CH_{3(c,d)}$),31.25($C_{1\cdot}$),57.9 (CH_2OH), 93.8 (C_3), 141.5 (CH), 160.5 (C_4). IR νcm^{-1} (KBr): ν_{OH} = 3280, $\nu_{C=C}$ = 1580.

Typical procedure for the synthesis of cyclopropenyl alcohols **5** *and* **6**: 500 mg of 3*H*-pyrazole **3** or **4c** was diluted in 100 ml of dry dichloromethane, and was irradiated at 300 nm in a Rayonet apparatus for 30 min. The starting colourless solution became dark red during the reaction. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica with dichloromethane as eluant to provide derivative **5** or **6**.

5: Yield: 75 %; mp: 145°C. Anal. Calcd for $C_{18}H_{18}O$: C: 86,4%, H: 7,2%, O: 6,4%, found: C: 86,2%, H: 7,1%, O: 6,2%; ms: 250 ((M^+), 74,3), 13,2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 6H, $CH_{3(a,b)}$); 3.93 (s, 1H, OH), 6.33 (s, 1H, =C-H); 7.28-7.38 (m, 10 H, H_{arom}). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 20.30 (CH_3,127.0–144.2 (C_{arom}), 93.80 (C_1),142.3 (C_2), 77.30 (C_6), 93.7 (C_3). IR νcm^{-1}(KBr): ν_{OH} = 3381, $\nu_{C=C}$ = 1499.

6: Yield: 70 %. Anal. Calcd for $C_9H_{16}O$: C: 77,14%, H: 11,42%, O: 11,42%, found: C: 77,1%, H: 11,3%, O: 11,4%; ms: 140 ((M^+), 83,3) ^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 1.30 (6H, s, CH_3 (a,b)), 1.79 (s, 3H, CH_3(c,d)),6.40 (s, 1H, OH), 4.82 (s, 2H, CH_2), 6.70 (1H, CH), 1.92 (s, 3H, CH_3(c,d). IR νcm^{-1} (KBr): ν_{OH} = 3418,$\nu_{C=C}$ =1443.

We are very grateful to Professor A. Romerosa for his help and to carry out 1D and 2D NMR analysis at the University of Almeria in Spain. This paper is dedicated to the memory of Najet, the sister of Dr Naceur Hamdi.

Received 11 January 2001; accepted 25 February 2005
Paper 05/3001

References

1 T. Katsuki, *Adv. Synth. Catal*., 2002, **344**, 131.
2 H.U. Reissig and R. Zimmer, *Chem. Rev*., 2003, **103**, 1151.
3 H. Lebel, J.F. Marcoux, C. Molinaro and A.B. Charrette, *Chem. Rev*., 2003, **103**, 977.
4 M.S. Baird and T. Schmidt in Carbocyclic *Three-Membred Ring Compounds*; A. de Meijere Ed., Georg Thieme Verlag: Stuttgart 1996, p.114.
5 M.S. Baird, *Cyclopropenes transformations; addition reactions*, Houben –Weyl; Thieme, Stuttgart, 1997, E17D/2.
6 L. Liao and J.M. Fox, *J. Am. Chem. Soc*., 2002, **124**, 14322.
7 M. Nakamura, A. Hirai and E. Nakamura, *J. Am. Chem. Soc*. 2000, **122**, 978.
8 H. Lehmkuhl and K. Mehler, *Justus Liebigs Ann. Chem*., 1978, 1841.
9 E. Nakamura, D. Machii and T. Imubushi, *J. Am. Chem. Soc*., 1989, **111**, 6849.
10 S. Yamago, S. Ejiri and E. Nakamura, *Chem. Lett*., 1994, 1889.
11 J.H. Rigby and P.Ch. Kierkus, *J. Am. Chem. Soc*., 1989, **111**, 4125.
12 Y.F. Zhu, T. Yamazaki, J.W. Tsang, S. Lok and M. Goodmann, J. *Org. Chem.*, 1992, **57**, 1074.
13 H. Nuske, S. Brase and A. de Meijere, *Synlett* 2000, 1467.
14 M.P. Doyle, M.A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley and Sons, New York, 1998.
15 M.P. Doyle, D. Eene, C.S. Peterson and V. Lynch, *Angew. Chem*., Int. Ed. 1999, **38**, 700.
16 H.M.L. Davies and H.G. Lee, *Org Lett*., 2004, **6**, 1233.
17 M.M. Diaz-Requejo, M.A. Mairena, T.R. Belderrain, M.C. Nicasio, S. Trofimenko and P.J. Perez., *Chem. Commun*., 2001, 1804–1805 and references therein.
18 A.F. Noels, A. Demonceau, N. Petiniot, A.J. Hubert and Ph. Teyssie, *Tetrahedron Lett*., 1982, **38**, 2733.
19 T.R. Hoye and G.J. Dinsonore, *Tetrahedron Lett*., 1991, **32**, 3755.
20 M. Vidal, M. Vincens and P. Arnaud, *Bull. Soc.Chim. Fr*., 1972, 657.
21 N. Hamdi and A. Khemiss, *J. Soc. Alger. Chim*., 2002, **12**, 45.
22 N. Hamdi, Y. Arfaoui and A. Khemiss unpublished results.
23 H.G. Richey Jr and R.M. Bension, *J.Org. Chem*., 1980, **45**, 5036.