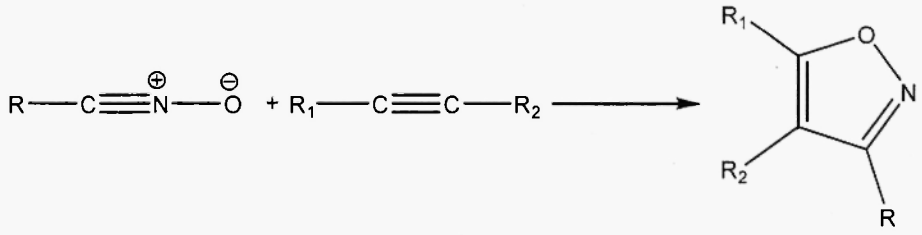
SYNTHESIS AND EVOLUTION OF NEW ISOXAZOLO-1,4-QUINONES OF BIOLOGIC INTEREST

Naoufel Ben Hamadi and Moncef Msaddek*
* Current address: Laboratoire de Synthèse Heterocyclique, Photochimie et Complexation. Département de Chimie, Faculte des Sciences 5000 Monastir (Tunisie). E-mail address:
E-mail : moncef.msaddek@fsm.rnu.tn

Abstract : In the exploration of synthesis and chemistry of isoxazoles, we found that the reaction of aromatic nitrile oxides with the Quinone derivatives produced isoxazolo-1,4-quinones is of considerable biological interest. The reductive cleavage of the N-O bond gave arylimidoyl-3-hydroxy-1,4-quinones.
Keywords: nitrile oxides; isoxazolo-1,4-quinones; imidoylquinones; pharmacological; biological activities.

Introduction

The addition of a 1,3-dipole to acetylenics and alkenes for the synthesis of five-membered rings is a classic reaction in organic chemistry (1-3). The 1,3-dipolar cycloaddition reaction of nitrile oxides to acetylenics is an effective procedure for the preparation of isoxazoles (4,5) (scheme-1), which are intermediates for the synthesis of nitrogen containing a natural product. Based on the literature evidence (6,7), the isoxazoles formed in the reaction between nitrile oxides and acetylenics are used building blocks; since they are readily converted into 3-hydroxycarbonyl compounds and β-hydroxy-ketons. Other useful functional groups, such as 3-aminoalcohols, may also be obtained from isoxazoles. Considerable attention has been given to the synthesis of isoxazoles, both for their high pharmacological and biological activites (8-12). The role of Quinone derivatives in antibacterial and ant-fungal drugs and growth accelerators for plants has been extensively investigated during the last three decades (13). A number of arylnaphthisoxazolediones and imidoylnaphthoquinones was synthesized and investigated in our laboratories (14-17). Some of imidoylnaphthoquinones show plant-growth regulating activity (17). In previous papers we have described the development of 1,3-dipolar cycloaddition (18,20). In this paper we describe the synthesis of a new isoxazolo-1,4-quinones and arylimidoyl-3-hydroxy-1,4-quinones. The key step encompasses 1,3-dipolar cycloaddition reactions which are developed in our laboratory (21).

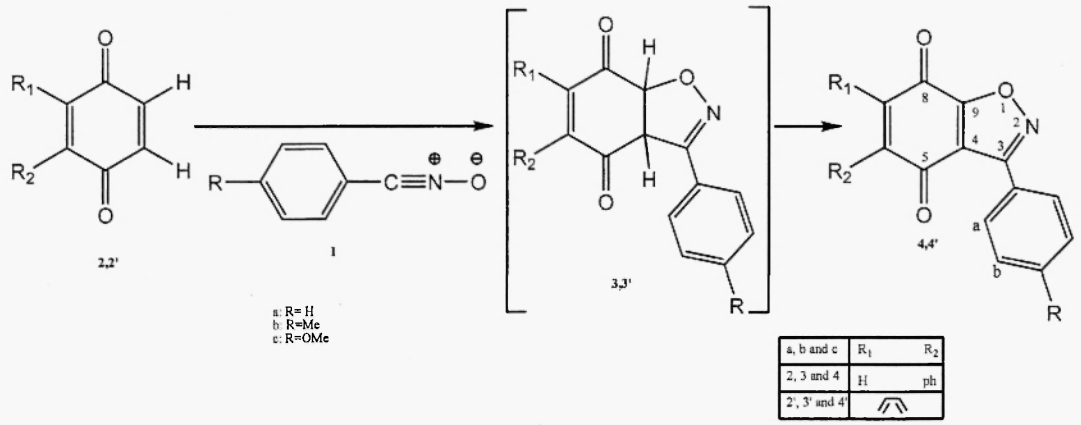


isoxazoles

Scheme-1

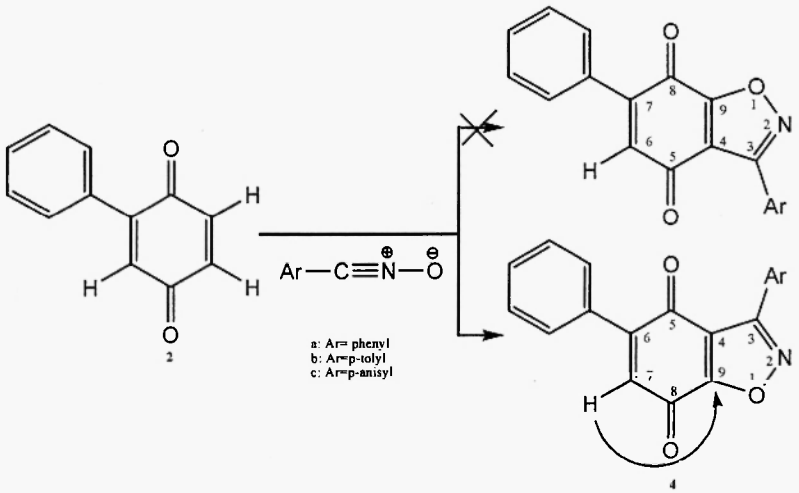
Results and Discussions

The method proposed is relatively very simple, the 1,3-dipolar cycloaddition reaction of in situ generated nitrile oxides **1** (22) with 1,4-quinones **2** and **2'** realized in refluxing toluene led to exclusive formation of the isoxazolo-1,4-quinones **4** and **4'** respectively. In the present case **4** and **4'** arises by oxidation of initial adduct **3** and **3'** (Scheme-2), presumably by the action of 1,4-quinones during the reaction, or by atmospheric oxygen during subsequent manipulations; similar behaviours are observed in addition of diphenyldiazomethane to 1,4-naphthoquinone **2** (23).



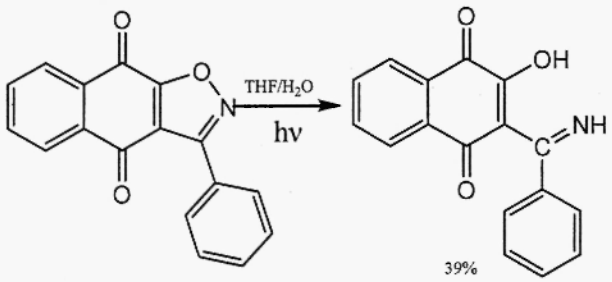
Scheme-2

The 1,3-dipolar cycloaddition of nitrile oxides with phenyl-1,4-benzoquinone **2** is, in each case, regiospecific. However, regiochemical assignments of all adducts were deduced from their HMBC 2D-NMR spectra. H_7 proton correlates only with the carbon atom C_9 (164.40 -165.30 ppm) (Scheme-3).



Scheme-3

The N-O bond proved unexpectedly to be resistant to reductive agents described in literature, including zinc-acetic acid system (24), catalytic hydrogenation over raney nickel (25) or Pd (26), lithium aluminium hydride (27,28) and sodium borohydride with either $NiCl_2.6H_2O$ or $CoCl_2.6H_2O$ (29,30). In 1973, Yukinaga et al. (16) published the irradiation of 3-phenyl-5,8-dihydronaphtho[2,3-d]-isoxazole-5,8-dione in aqueous tetrahydrofuran, using Hg lamp, which leads to the exclusive formation of 2-benzimidoyl-3-hydroxy-1,4-naphthoquinone (Scheme-4).

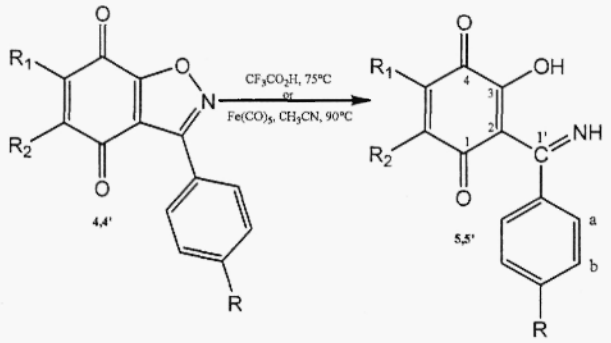


Scheme-4

Reduction of isoxazolo-1,4-quinones **4** and **4'** to the arylimidoyl-3-hydroxy-1,4-quinones **5** and **5'** respectively, was cleanly achieved by using trifluoroacetic acid. As a recently transition-metal carbonyls (6,31) have been used efficiently to reduce closely related isoxazoles, we have now successfully utilized $Fe(CO)_5$ for reductive cleavage of isoxazoles in high yield. Results are shown in Table-1.

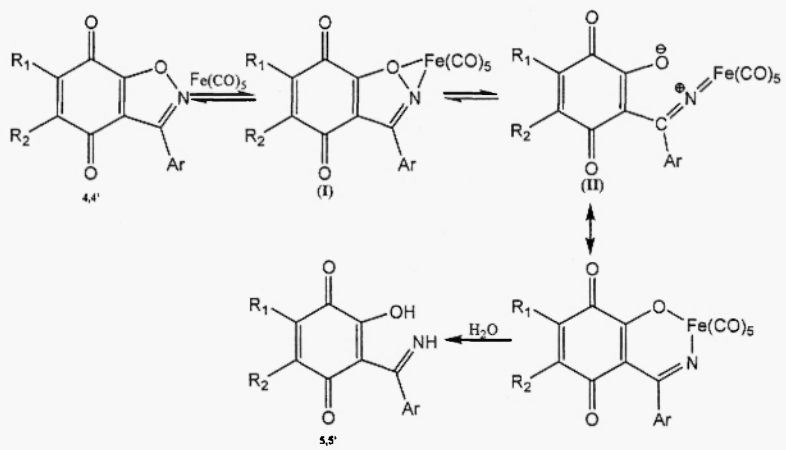
Imidoylquinones were characterized by IR, MS and NMR. Absorption bands for C=N, NH and OH groups were detected in the IR spectra. Additionally, their ^{1}H-NMR spectra revealed the presence of signals for NH and OH which disappear later when adding D_2O.

Table-1 : Reduction of isoxazolo-1,4-quinones using $Fe(CO)_5$ or CF_3CO_2H.



Entry	isoxazolo-1,4-quinones			yield using	
	R	R_1	R_2	$Fe(CO)_5$	or CF_3CO_2H
1	H	H	ph	90	80
2	CH_3	H	ph	75	65
3	OCH_3	H	ph	85	60
4	H			60	40
5	CH_3			90	70
6	OCH_3			80	55

The proposed mechanism of the reductive cleavage of isoxazoles is similar to the mechanism suggested by Nitta and kobayashi [6]. The back-donation from a π d filled orbital of fer to the lumo π^* of isoxazoles, which should facilitate the N-O bond cleavage. The intermediate II should be also formed rapidly, via the σ-complex I. Water is then responsible for the decomposition of the complex II (Scheme-5)



Scheme-5

In summary, we have developed an alternative procedure, to the arylimidoyl-3-hydroxy-1,4-quinones. Further generalisation of these results, their implication for the synthesis of various imidoyls products. The biological evaluation of this compound is in progress.

Experimental Section

Generalities: Infrared spectra were recorded on PERKIN-ELMER IR-197 infrared spectrometer. Mass spectra were determined on a NIERJOHNSON MS80RF spectrometer. Melting points were determined on a BUCHI-510 capillary melting point apparatus. Thin layer chromatography (TLC) was performed on silica gel 254 plates (Merck) with UV (254 nm) visualisation whereas chromatographic separations were conducted on silica gel Si-60-7734 Merck using water-Jacketed columns. ^{1}H NMR and ^{13}C NMR spectra recorded at 300 MHz and 75.64 MHz, respectively. Coupling constants are given in Hz and alchemical shifts are relative to an internal standard of tetramethylsilane. Toluene was distilled from and stored over sodium wire.

General procedure for nitrile oxides cycloaddition to 1,4-quinones
Et_3N (1.8 equiv) was added **portionwise** to a stirred solution of 1,4-quinones **2, 2'** and chloroxime in toluene at 110°C, and the mixture stirred for 3h and concentrated to give a brown oil which was subjected to rapid silica filtration to give the isoxazolo-1,4-quinones **4** and **4'**. Recrystallization from dichloromethane/light petroleum, as solids.

3-Phenyl-5,8-dihydronaphtho[2,3-d]-isoxazole-5,8-dione 4a: Yellow crystals yield 75%, m.p. 132°C; MS, m/z (%) :[$M^{+\cdot}$, 275], 94 (100%). IR (KBr) ν_{cm-1}; 1630 (C=N); ^{1}H NMR ($CDCl_3$, 300 MHz)δ: 7.46-8.21 (m, 9H, H_{arom}), ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 118.55-134.31 ($C_{arom,4}$), 159.98 (C_3), 165.26 (C_9), 172.32 (C_5), 177.63 (C_8).

3-Tolyl-5,8-dihydronaphtho[2,3-d]-isoxazole-5,8-dione 4b: Yellow crystals yield 62%, m.p. 138°C; MS, m/z (%) :[$M^{+\cdot}$, 289], 175 (100%). IR (KBr) ν_{cm-1}; 1630 (C=N); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.38 (s, 3H, CH_3), 7.27 (d, 2H, H-b) and 7.97 (d, 2H, H-a): AA'BB' patt. J= 7.8 Hz, 7.73-8.22 (m, 4H, H_{arom}), ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.57 (CH_3), 118.57-140.71 ($C_{arom,4}$), 159.96 (C_3), 165.21 (C_9), 172.39 (C_5), 177.68 (C_8).

3-Anisyl-5,8-dihydronaphtho[2,3-d]-isoxazole-5,8-dione 4c: Yellow crystals yield 69%, m.p. 141°C; MS, m/z (%) :[$M^{+\cdot}$, 305], 251 (100%). IR (KBr) ν_{cm-1}; 1635 (C=N); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.83 (s, 3H, OCH_3), 7.00 (d, 2H, H-b) and 8.12 (d, 2H, H-a): AA'BB' patt. J= 9 Hz, 7.74-8.22 (m, 4H, H_{arom}), ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 54.40 (OCH_3), 113.09-161.91 ($C_{arom,4}$), 159.61 (C_3), 161.01 (C_9), 172.44 (C_5), 177.82 (C_8).

3,6-Diphenyl-5,8-dihydrobenzo[2,3-d]-isoxazole-5,8-dione 4'a: Brown crystals yield 71%, m.p. 131°C; MS, m/z (%) :[$M^{+\cdot}$, 301], 201 (100%). IR (KBr) ν_{cm-1}; 1630 (C=N); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.91 (s, 1H, H_5), 7.39-7.79 (m, 10H, H_{arom}), ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 118.42-133.89 ($C_{arom,6,7}$), 118.31 (C_4), 161.88 (C_3), 165.30 (C_9), 173.29 (C_5), 180.52 (C_8).

6-Phenyl-3-tolyl-5,8-dihydrobenzo[2,3-d]-isoxazole-5,8-dione 4'b: Yellow crystals yield 67%, m.p. 152°C; MS, m/z (%): [M^+, 315], 132 (100%). IR (KBr) ν_{cm-1}; 1630 (C=N); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.37 (s, 3H, CH_3), 6.90 (s, 1H, H_5), 7.26 (d, 2H, H-b) and 7.87 (d, 2H, H-b): AA'BB' patt. J= 7.8 Hz, 7.61 (s, 5H, H_{arom}), ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.37 (CH_3), 116.37-139.61 ($C_{arom,6,7}$), 118.10 (C_4), 160.91 (C_3), 164.40 (C_9), 173.21 (C_5), 179.97 (C_8).

3-Anisyl-6-phenyl-5,8-dihydrobenzo[2,3-d]-isoxazole-5,8-dione 4'c: orange crystals yield 70%, m.p. 163°C; MS, m/z (%): [$M^{+\cdot}$, 331], 245 (100%). IR (KBr) ν_{cm-1}; 1635 (C=N); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.88 (s, 3H, OCH_3), 6.95 (s, 1H, H_5), 7.00 (d, 2H, H-b) and 8.10 (d, 2H, H-a): AA'BB' patt. J= 9 Hz, 7.49 (s, 5H, H_{arom}), ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.48 (OCH_3), 114.16-162.09 ($C_{arom,6,7}$), 118.29 (C_4), 160.22 (C_3), 164.93 (C_9), 174.78 (C_5), 180.48 (C_8).

Methods used to carry out reductive cleavage

Method A:

Cycloadduits **4** and **4'** in trifluoroacetic acid (10 mL) was refluxed for 5-6h and then poured into a ice-water mixture (50 mL). After extraction with $CHCl_3$ (3 × 50 mL), the layers were separated, and the organic phase was washed with satd aq $NaHCO_3$ (3 × 10 mL), then with water (3 × 10 mL), and finally dried Na_2SO_4, and evaporated in vacuo. The crude products were purified by crystallization from EtOH.

Method B:

A mixture of 1 mmole of isoxazole, 1 mmole of $Fe(CO)_5$, 1 mL of water and 15 mL of MeCN is refluxed under nitrogen for 1-2h. The resulting crude was chromatographed on a silica gel column. Recrystallization from ethanol, as a solid.

2-Benzimidoyl-3-hydroxy-1,4-naphthoquinone 5a: Yellow crystals, m.p. 258°C; MS, m/z (%) :[$M^{+\cdot}$, 277], 94 (100%). IR (KBr) ν_{cm-1}; 1665 (C=N); 3300 (N-H and O-H); ^{1}H NMR (DMSO, 300 MHz) δ: 7.41-8.05 (m, 9H, H_{arom}), 10.11 (br s, 1H, NH), 11.77 (br s, 1H, OH), ^{13}C NMR (DMSO, 75 MHz) δ: 109.09-137.07 ($C_{arom,2}$), 175.32 ($C_{1'}$), 177.35 (C_3), 181.70 (C_1), 181.90 (C_4).

2-(p-Methylbenzimidoyl)-3-hydroxy-1,4-naphthoquinone 5b: Yellow crystals, m.p. 247°C; MS, m/z (%) :[M^+, 291], 179 (100%). IR (KBr) ν_{cm-1}; 1660 (C=N); 3330 (N-H and O-H); ^{1}H NMR (DMSO, 300 MHz) δ: 2.37 (s, 3H, CH_3), 7.23-8.03 (m, 8H, H_{arom}), 10.03 (br s, 1H, NH), 11.67 (br s, 1H, OH), ^{13}C NMR (DMSO, 75 MHz) δ: 21.51 (CH_3), 109.31-140.68 ($C_{arom,2}$), 175.47 ($C_{1'}$), 177.30 (C_3), 181.77 (C_1), 182.17 (C_4).

2-(p-Methoxybenzimidoyl)-3-hydroxy-1,4-naphthoquinone 5c: Yellow crystals, m.p. 236°C; MS, m/z (%) :[M^+, 307], 41 (100%). IR (KBr) ν_{cm-1}; 1650 (C=N); 3320 (N-H and O-H); ^{1}H NMR (DMSO, 300 MHz) δ: 3.82 (s, 3H, OCH_3), 6.98 (d, 2H, H-b) and 7.38 (d, 2H, H-a): AA'BB' patt. J= 9 Hz, 7.74-8.04 (m, 4H, H_{arom}), 10.01 (br s, 1H, NH), 11.58 (br s, 1H, OH), ^{13}C NMR (DMSO, 75 MHz) δ: 55.89 (OCH_3), 109.29-161.86 ($C_{arom,2}$), 174.93 ($C_{1'}$), 177.16 (C_3), 181.68 (C_1), 182.32 (C_4).

2-Benzimidoyl-3-hydroxy-5-phenyl-1,4-benzoquinone 5'a: Brown crystals, m.p. 180°C; MS, m/z (%) :[$M^{+\cdot}$, 303], 43 (100%). IR (KBr) ν_{cm-1}; 1655 (C=N); 3300 (N-H and O-H); ^{1}H NMR (DMSO, 300 MHz) δ: 6.89-7.15 (m, 11H, $H_{arom,6}$), 9.90 (s, 1H, NH), 11.29 (s, 1H, OH), ^{13}C NMR (DMSO, 75 MHz) δ: 109.09-137.07 ($C_{arom,2,5,6}$), 175.32 ($C_{1'}$), 177.35 (C_3), 181.70 (C_1), 181.90 (C_4).

2-(p-Methylbenzimidoyl)-3-hydroxy-5-phenyl-1,4-benzoquinone 5'b: Brown crystals, m.p. 165°C; MS, m/z (%) :[$M^{+\cdot}$, 315], 131 (100%). IR (KBr) ν_{cm-1}; 1650 (C=N); 3335 (N-H and O-H); ^{1}H NMR (DMSO, 300 MHz) δ: 2.29 (s, 3H, CH_3), 6.93-7.13 (m, 10H, $H_{arom,6}$), 9.96 (s, 1H, NH), 11.35 (s, 1H, OH), ^{13}C NMR (DMSO, 75 MHz) δ: 21.51 (CH_3), 109.31-140.68 ($C_{arom,2.5.6}$), 175.47 ($C_{1'}$), 177.30 (C_3), 181.77 (C_1), 182.17 (C_4).

2-(p-Methoxybenzimidoyl)-3-hydroxy-5-phenyl-1,4-benzoquinone 5'c: Brown crystals, m.p. 128°C; MS, m/z (%) :[$M^{+\cdot}$, 333], 231 (100%). IR (KBr) ν_{cm-1}; 1660 (C=N); 3330 (N-H and O-H); ^{1}H NMR (DMSO, 300 MHz) δ: 3.82 (s, 3H, OCH_3), 6.91-7.42 (m, 10H, $H_{arom,6}$), 9.89 (br s, 1H, NH), 11.31 (br s, 1H, OH), ^{13}C NMR (DMSO, 75 MHz) δ: 55.75 (OCH_3), 109.29-161.86 ($C_{arom,2,5,6}$), 174.93 ($C_{1'}$), 177.16 (C_3), 181.68 (C_1), 182.32 (C_4).

References

1. T. Curtius, *Ber. Dtsch. Chem. Ges.* **16**, 2230, (1883).
2. E. Buchner, *Ber. Dtsch. Chem. Ges.* **21**, 2637, (1888).
3. K.B. Torssell and G. Nitrile, Oxides, Nitrones and Nitronates in Organic Synthesis VCH. (1988).
4. T. Back, G. Bethell, R.J. Parvez, M. Taylor and J.A. Wehrli, *D. J. Org. Chem.*, **64**, 7426-7432, (1999).
5. R.A. Abramovitch, A. Deeb, D. Kishore, G.B. Mpango and W. Shinkai, *I. Gazz. Chim. Ital.* **118**, 167-171, (1998).
6. M. Kobayashi Nitta, *T. J. Chem. Soc. Perkin Trans. I.* 1401, (1985).
7. A.K. Soufiaoui Bennani, M. Kerbal, A. Fkih Tetouani and N.S. Biti, *Tetrahedron* **51**, 10923, (1995).
8. K. Sekido Kobinata, S. Uramoto, M. Ubukata, M. Osada, H. Yamaguchi, I. Isono, *K. Agric. Biol. Chem.* **55**, 1415-1416, (1991).
9. S. Arneric, P. Sullivan J, P. Briggs C, A. Donnelly-Roberts, D. Anderson D, J. Raszkiewicz J, L. Hughes M, L. Cadman E, D. Adams, P. Garvey D, *S. J. Pharmacol. Exp. Ther.* **270(1)**, 310-318, (1994).
10. A. Rockwell, L. Rafalski, M. Pitts, W, J. Batt, D, G. Petraitis, J, J. Degrado, W, F. Mousa, S. Jadhav, P, *K. Bioorg. Med. Chem. Lett.* **9**, 937, (1999).
11. Y. Kang, K. Yoo, K, H. Seo, K, J. Hong, C, Y. Lee, C, S. Park, S, Y. Kim, D, J. Park, S, *W. Bioorg. Med. Chem. Lett.* **10**, 95, (2000).
12. F. Janssen, W. Jusko, W, J. Chang, S, T. Kirkman, S, *K. Chim. Pharmacol. Ther.* **27**, 352, (1980).
13. H. Kano, Ogata, M. Yukinaga, H. JP 71-7502 19710218. CAN 77:152158 AN 1972:552158.
14. S. Morrocchi, Quilico, A. Ricca, A. Selva, *A. Gazz. Chim. Ital.* **98(8-9)**, 891-906, (1968).
15. G. Rao Brahmeshwari, V. Rajeswar, Rao, T. V. Padmanabha. *Indian J. Chem.* Sec.B: Organic **34B(2)**, 139-140, (1995).
16. M. Matsumoto Gata, H. Kano, H. Yukinaga, *H. J. Chem. Soc. Chem. Comm.* **6**, 218-219, (1973).
17. H. Yukinaga, Ogata, M. Kano, H. ZA 75-6575 19751017. CAN 87:5721 AN 1977:405721.
18. F. Msaddek Djapa, M. Ciamala, K. Vebrel, J. Riche, *C. Eur. J. Chem.* 1271-1278, (2000).
19. J. Msaddek Vebrel, M. Djapa, F. Ciamala, K. Laude, *B. Eur. J. Chem.* 2855-2859, (1998).
20. M. Rammah Msaddek, M. Ciamala, K. Vebrel, J. Laude, *B. synthesis* **12**, 1495-1498, (1997).
21. M. Rammah Msaddek, , M. Ciamala, K. Vebrel, J. Laude, *B. Bull. Soc. Chim. Belg.* **106**, 825-831, (1997).
22. M. Christl, *Huisgen. R. Chem. Ber.* **106**, 3345, (1973).
23. A. Bader, M.R. Ettling, *G. J. Am. Chem. Soc.* **75**, 730, (1953).
24. Wovkulich. P.M. Uskokovic. M.R. *Tetrahedron* **41**, 3455, (1985).
25. T. Hirai Koizumi, H. Yoshii, *E. J. Org. Chem.* **47**, 4004, (1982).
26. H. Kasahara Lida, K. Kibayashi, *C. J. Am. Chem. Soc.* **108**, 4647, (1986).
27. R. Hauck Huisgen, H. Grashey, R. Seidl, *H. H. Chem. Ber.* **102**, 736, (1969).
28. W. Petrzilka Oppolzer, *M. J. Am. Chem. Soc.* **98**, 6722, (1976).
29. M. Cinquini Annunziata, F. Cozzi, A. Gilardi. Restelli, *A. J. Chem. Soc. Perkin Trans.* **1**, 2289, (1985).
30. K. Collington Amstrong, W. Knight, G. Naylor, A. Warren, *S. J. Chem. Soc. Perkin Trans.* **1**, 1433-1447, (1993).
31. S. Goti Cicchi, A. Brandi, A. Guarna, A.: De Sarlo. F. *Tetrahedron Lett.* **31**, 3354-3351, (1990).

Received on April 10, 2006