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Dedicated to the memory of
Professor Ioan Silaghi-Dumitrescu (1950 – 2009)

SYNTHESIS OF 3-TERT-BUTYL-5-(4-VINYLPHENYL)-1,2,4-OXADIAZOLE USING TWO DIFFERENT PATHWAYS

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3-tert-butyl-5-(4-vinylphenyl)-1,2,4-oxadiazole (1) has been synthesized in two different ways, using 3-tert-butyl-5-(4-ethynylphenyl)-1,2,4-oxadiazole (2) or 4-(3-tert-butyl-1,2,4-oxadiazol-5-yl)benzaldehyde (3) as intermediates. The structure of compound 3 was confirmed by X-ray diffraction. 1,2,4-Oxadiazoles have been prepared using 1,1-carbonyldiimidazole (CDI) as a reagent for both formation and cyclodehydration of *O*-acyl-amidoximes. The use of CDI facilitates parallel purification of the oxadiazole products by simple liquid-liquid extraction and filtration. The heterocycles were obtained in good yields and in relatively short reaction times.

INTRODUCTION

Oxadiazoles have often been described as bioisosteres of amides and esters.[1] The increased hydrolytic[2] and metabolic stability of the oxadiazole ring, the improved pharmacokinetic and the *in vivo* performance make this heterocycle an important structural motif in the pharmaceutical industry. As a consequence of these characteristics, oxadiazoles have played an important role in numerous drug discovery programs, including muscarinic agonists,[3] benzodiazepine receptor partial agonists,[4] dopamine transporters,[5] antirhinovirals,[6] growth hormone secretagogues,[7] and 5-HT receptor agonists.[8] They are also reported as inhibitors of tyrosine kinase,[9] baterial and human DNA topoisomerases,[10] and human neutrophil elastase.[11]

Until now, 1,2,4-oxadiazoles have been most commonly synthesized in solution or on solid support in a two-step process by reaction of amidoximes and activated carboxylic acid derivatives.

GENERAL DISCUSSION

In the first step, the amidoxime is *O*-acylated by the activated carboxylic acid derivative, which can be previously prepared or *in situ* activated by several methods including the use of the acyl chloride,[12] acyl fluoride,[13] symmetrical anhydride,[14] active ester,[9] ester with sodium ethoxide,[15] N,N′-carbonyldiimidazole (CDI),[16] acyl palladium complexes,[17] dicyclohexylcarbodiimide (DCC),[14a,18] 2-(dimethylamino)-isopropyl chloride (DIC),[19] 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide (EDC),[10,12,14a] bis(2-oxo-3-oxazolidinyl) phosphinic

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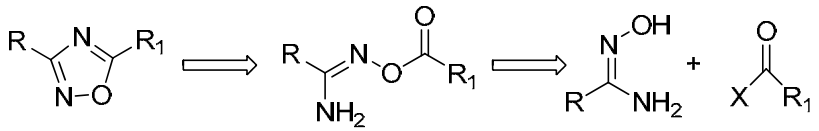
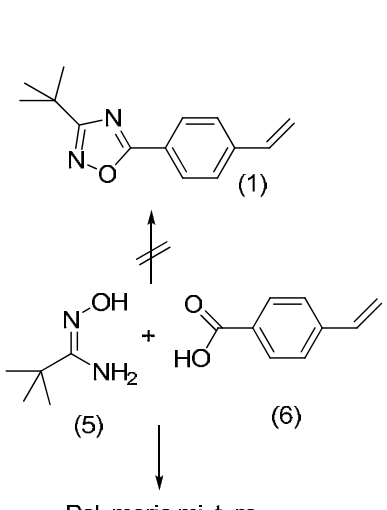
chloride (BOP-Cl)[14a] and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU).[20] The *O*-acylated amidoxime can be isolated or immediately undergo a cyclodehydration reaction. The heterocyclic ring is usually formed by heating to temperatures above 100 °C. Microwave techniques have also been employed in the synthesis of such heterocycles (Scheme 1).

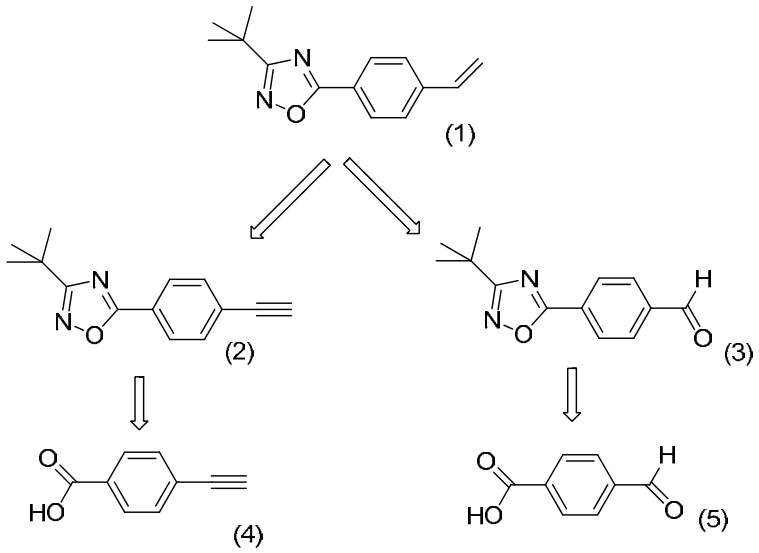
However this method does not work for all carboxylic acid derivatives because of the nature of the substituent. For example the 3-tert-butyl-5-(4-vinylphenyl)-1,2,4-oxadiazole (1) cannot be obtained using the corresponding 4-vinylbenzoic acid (6) using the general method. In this case the cyclisation takes place, but a polymeric mixture of the oxadiazole compound is formed (Scheme 2).



Scheme 1 – General retrosynthetic analysis of the preparation of oxadiazoles.



Scheme 2 – General synthesis for (1).



Scheme 3 – Retrosynthetic routes of 3-tert-butyk-5-(4-vinylphenyl)1,2,4-oxadiazole (1).

For this reason we had to find other ways to synthesize compound (1). Two alternative, synthetic routes using as intermediates 3-tert-butyl-5-(4-ethynylphenyl)-1,2,4-oxadiazole (2) and 4-(3-tert-butyl-1,2,4-oxadiazol-5-yl)benzaldehyde (3) are shown in scheme 3. For one of the routes we consider the selective hydrogenation of (2) with Lindlar catalyst. The disadvantage of this method is that in the final step a mixture of (1) and 3-tert-butyl-5-(4-ethylphenyl)-1,2,4-oxadiazole (7) is obtained. For the second synthesis the acid (5) is commercially available but the yields are lower.

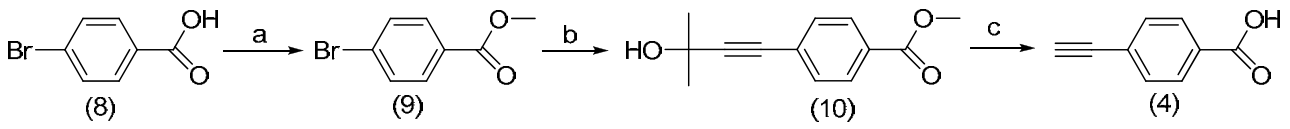
RESULTS

Synthesis of 4-ethynylbenzoic acid(4) (EBA)

Because EBA (4-ethynylbenzoic acid) (4) was used on a multigram scale and is expensive, we had to synthetise it.[21] A modified synthetic route was developed that is much cheaper and faster than previous methods and gives essentially quantitative yields. We took advantage of the sensitivity of the ester linkage toward potassium or sodium hydroxide to cleave the 2-hydroxypropyl group and saponify the ester simultaneously in l-butanol or 2-propanol to prepare EBA in high yield.

Methyl p-bromobenzoate (MBB) (8) was coupled with 2- methyl-3-butyn-2-ol (9) using Pd(O)/CuI catalysis to give the intermediate 4-(4-(methoxycarbonyl)-phenyl)-2-methyl-3-butyn-2-ol (10). MBB was mixed with a small excess of MEBYNOL in deaerated, dried triethylamine/ pyridine (volume ratio 5/2) in the presence of catalytic amounts of dichloro-bis(triphenylphosphine) palladium, triphenylphosphine, and cuprous iodide, and the solution was refluxed; the sodium or potassium salt of EBA precipitated quantitatively from the solution.

Crystalline EBA changes color on standing from white to off-white and then to light tan, showing that is not very stable at room temperature and light (it polymerizes slowly). However, its sodium and potassium salts are stable.

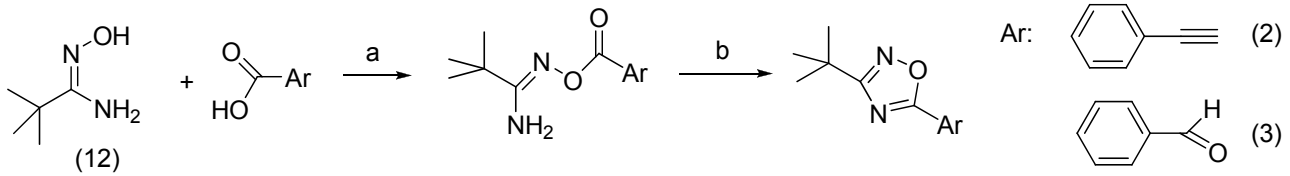


a: MeOH, H_2SO_4, reflux; b: $HOC(CH_3)_2CCH$, $PdCl_2(Ph_3P)_2$, Et_3N; c: i. NaOH, 1-BuOH, reflux; ii. HCl

Scheme 4 – Synthesis of oxadiazoles (2) and (3).

Generation of oxadiazoles

The general approach to parallel solution-phase synthesis of 1,2,4-oxadiazoles is summarised in Scheme 5. Carboxylic acids were activated with CDI in DMF at room temperature and treated with amidoximes in DMF. The tert-butyl amidoxime was prepared from trimethyl acetonitrile and hydroxylamine by refluxing in 2-propanol.



a CDI, DMF, r.t.; b CDI, DMF, reflux

Scheme 5 – Synthesis of oxadiazoles (2) and (3).

Activation of the carboxylic acid moiety with CDI and further acylation of the amidoxime in DMF as solvent furnished the *O*-acylamidoxime, which was not isolated; on heating to 120 °C for five hours, it underwent a cyclodehydration reaction, delivering the 1,2,4-oxadiazole derivative in 73% yield after purification. It was gratifying that the substituent at the position 4 was not affected under these conditions.

All the 1,2,4-oxadiazoles were obtained in good yields for the two acids studied. The nature of the side chain plays a significant role in terms of conversion to the desired heterocycle, since the results obtained were quite different. The tert-butyl group of the amidoxime does not exert a strong influence on the heterocycle formation.

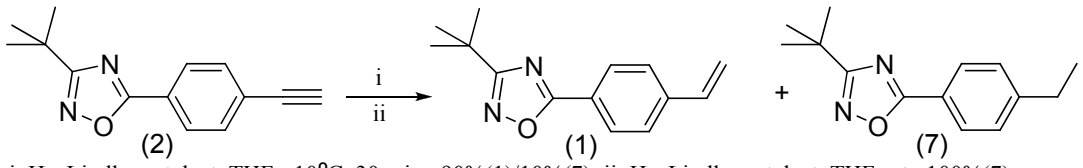
Establishing the vinyl group

In the next step the ethynyl heterocycle was hydrogenated in the presence of Lindlar catalyst. At low temperature (-10°C) and for a short reaction time (30 min), using THF as solvent, the required vinyl oxadiazole was obtained as the major product. If the temperature (higher) and the time (longer) are different, the hydrogenation was more and more dominated by the ethyl derivate. After 2h at room temperature the hydrogenation was completed to the 3-tert-butyl-5-(4-ethylphenyl)-1,2,4-oxadiazole. The formation of compound (7) cannot be avoided, and it cannot be separated from (1) because of similar polarities. However, after 0,5h/-10°C not all the alkyne was hydrogenated (Scheme 6).

The second route to 3-tert-butyl-5-(4-vinylphenyl)-1,2,4-oxadiazole (1) started from 4-(3-tert-butyl-1,2,4-oxadiazol-5-yl)-benzaldehyde (3) via a Wittig reaction using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as base.[22]

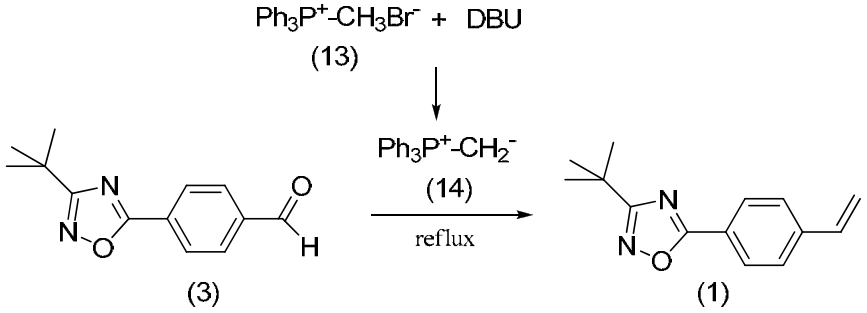
The reaction of methyltriphenyl-phosphonium bromide (13) with DBU in refluxing tetrahydrofuran or toluene afforded methylenetriphenylphosphorane (14), which further reacted with benzaldehydes to give styrenes in good yields.

Several amine bases (triethylamine, pyridine, DBN and DBU) were tested for the synthesis of 3-tert-butyl-5-(4-vinylphenyl)-1,2,4-oxadiazole (1) by reactions with methyltriphenylphosphonium bromide (13) and 4-(3-tert-butyl-1,2,4-oxadiazol-5-yl)-benzaldehyde (3). When DBU was used as a base, it was obtained in a high yield. Other bases did not lead to the desired products (in refluxing THF, in the same quantities).



i: H_2, Lindlar catalyst, THF, -10°C, 30 min., 90%(1)/10%(7); ii: H_2, Lindlar catalyst, THF, r.t., 100%(7)

Scheme 6 – Hydrogenation of 3-*tert*-butyl-5-(4-ethynyphenyl)-1,2,4-oxadiazole.



Scheme 7 – Synthesis of 3-*tert*-butyl-5-(4-ethynyphenyl)-1,2,4-oxadiazole (1) by Wittig reaction.

The solid-state structure of 3 was established by X-ray diffraction analysis and is shown in Figure 1. Compound 3 crystallizes in the monoclinic space group $P2_1/m$ with two molecules in the unit cell; most of the molecule except for the methyl group at C4 lies in the crystallographic mirror plane. The molecule presents a C12-O2 double bond (1.2039(14) Å), with an angle C9-C12-O2 of 124.87(11)°. In the five-membered ring, the bond length C1-N1 is 1.3099(14) Å, which is considerably shorter than the C1-N2 bond 1.3847(12) Å and thus confirms the double bond character of C1=N1.

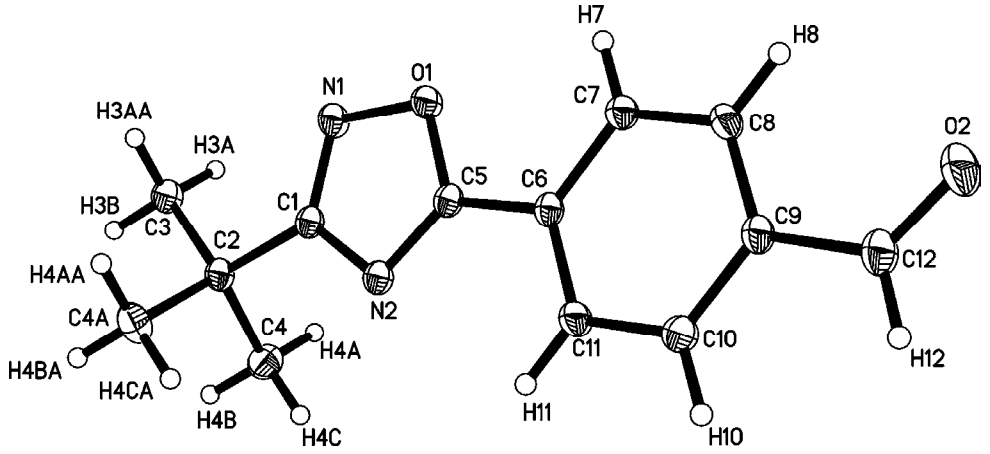


Fig. 1 – Molecular structure of 4-(3-tert-butyl-1,2,4-oxadiazol-5-yl)benzaldehyde (3). Atoms are drawn as 50% thermal ellipsoids. Selected bond lengths [Å] and angles [°]: C1-N1 1.3099(14), C1-N2 1.3847(12), N1-O1 1.4217(11), C5-O1 1.3455(12), C5-N2 1.3006(13), C12-O2 1.2039(14), C9-C12-O2 124.87(11).

EXPERIMENTAL

Synthesis of 4-(4-(Methoxycarbonyl)pheny1)-2methyl-3-butyn-2-ol (10)

Dichlorobis(triphenylphosphine)palladium (0.48 g, 0.68 mmol) was added under N_2 to a solution of Ph_3P (1.74 g, 6.6 mmol), CuI (0.48 g, 2.4 mmol), methyl p-bromobenzoate (124.6 g, 580 mmol), and MEBYNOL (58g, 690 mmol) in 800 mL of dry Et_3N and 320 ml of dry pyridine and refluxed under N_2 for 40 min. The mixture was cooled to r.t. and filtered to remove the insoluble triethylamine hydrobromide. The salt was washed with triethylamine and ethyl ether until the ether washings were clear. The combined filtrates were reduced to dryness under reduced pressure. The obtained solid was stirred twice with H_2O and then with 1L of 3% HCl and again twice with H_2O. The mixture was filtered, and the residue was dried under vacuum to yield 1**,** light tan color (123.82 g, 98% yield). Compound (10) was recrystallized from a small volume of toluene to give off-white crystals.

MS: *m*/*z* = 218 (M^+). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 – 7.89 (m, 2H), 7.48 – 7.38 (m, 2H), 3.91 (s, 3H), 2.86 (s, 1H), 1.63 (s, 6H).

Synthesis of p-Ethynylbenzoic Acid (4). (1.65 mol) of sodium hydroxide were dissolved in refluxing 1-butanol (2.6L); 90 g (0.41 mol) of 1 were added at once, and the mixture was refluxed for 10 min. After being cooled in an ice-bath the solution was filtered; the white residue was stirred with refluxing 2-propanol (600 mL) twice and dried at 60ºC under vacuum to give the sodium salt of EBA (78.5% yield). The hydrolysis-deprotection reaction was complete after 2 h at reflux using KOH (4 equiv), 6% w/v in 2-propanol.
MS: *m*/*z* = 146 (M^+). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.06 (d, *J* = 8 Hz, 2H), 7.59 (d, *J* = 8 Hz, 2H), 3.27 (s, 1H);

Synthesis of 3-tert-butyl-5-(4-ethynylphenyl)-1,2,4-oxadiazole (2). p-Ethynylbenzoic acid (4) was dissolved under an inert atmosphere in DMF and 1.1 equivalents of CDI were added. After 30 minutes of stirring at room temperature 1,1 equivalents of tert-butylamidoxime were added. A second portion of CDI (1.1 eq.) was added and the reaction mixture was heated to reflux until the reaction was complete. The mixture was cooled to room temperature and poured into a water-ice mixture. The solid thus formed was filtered off, washed with water, dried and flash chromatographed with ethyl acetate/hexane. MS: *m*/*z* = 226 (M^+) ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.13 – 8.05 (m, 2H), 7.66 – 7.58 (m, 2H), 3.26 (s, 1H), 1.43 (s, 9H).

Synthesis of 4-(3-tert-butyl-1,2,4-oxadiazol-5-yl)benzaldehyde (3). 4-vinyllbenzoic acid (6) was dissolved under an inert atmosphere in DMF and 1.1 equivalents of CDI were added. After 30 minutes of stirring at room temperature 1.1 equivalents of tert-butylamidoxime were added. A second portion of CDI (1.1 eq.) was added and the reaction mixture was heated to reflux until the reaction was complete. The mixture was cooled to room temperature and poured into a water-ice mixture. The solid thus formed was filtered off, washed with water, dried and flash chromatographed with ethyl acetate/hexane. MS: *m*/*z* = 230 (M^+) ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.35 – 8.28 (m, 2H), 8.06 – 8.00 (m, 2H), 1.45 (s, 9H).

Synthesis of 3-tert-butyl-5-(4-vinylphenyl)-1,2,4-oxadiazole (1). Method 1: 3-tert-butyl-5-(4-ethynylphenyl)-1,2,4-oxadiazole (2) was dissolved in THF and cooled to -10ºC. To this solution Lindlar catalyst was added and hydrogen was bubbled through the mixture for 30 minutes. The progress of the reaction was monitored by ^{1}H-NMR. The mixture was filtered over silica gel, the silica gel was washed with diethyl ether and the organic phases were evaporated. Method 2: a stoichiometric amount of 4-(3-tert-butyl-1,2,4-oxadiazol-5-yl)benzaldehyde (3), DBU and Br-methyltriphenylphosphine were dissolved in THF and heated to 50ºC for 3 hours. The reaction mixture was filtered over silica gel, the silica gel was washed with diethyl ether and the organic phases were evaporated. The product was flash chromatographed with ethyl acetate/hexane.
MS: *m*/*z* = 228 (M^+) ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.13 – 8.02 (m, 2H), 7.57 – 7.46 (m, 2H), 6.75 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.87 (dd, *J* = 17.5, 0.6 Hz, 1H), 5.44 – 5.33 (m, 1H), 1.43 (d, *J* = 1.5 Hz, 9H).

Synthesis of 3-tert-butyl-5-(4-ethylphenyl)-1,2,4-oxadiazole (7). 3-tert-butyl-5-(4-ethynylphenyl)-1,2,4-oxadiazole (2) was dissolved in THF. To this solution Lindlar catalyst was added and hydrogen was bubbled through the solution for 1 hour. The reaction progress was monitored by ^{1}H-NMR. The mixture was filtered over silica gel, the silica gel was washed with diethyl ether and the organic phases were evaporated. MS: *m*/*z* = 230(M^+). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.20 – 7.09 (m, 2H), 2.55 (q, *J* = 7.6 Hz, 2H), 1.31 (s, 9H), 1.18 – 1.03 (m, 3H).

X-ray Crystal Structure Determination (of 3): Data were recorded on an Oxford Diffraction Xcalibur area detector at low temperature using Mo-*K*α radiation (λ = 0.71073 Å). The structure was refined anisotropically using the program SHELXL-97[23]. Hydrogen atoms were refined freely using diatance restraints (at C3), included using rigid methyl groups (at C4) or using a riding model (all other H).
Crystal data for 3: $C_{13}H_{14}N_2O_2$, M_r = 230.26, monoclinic, space group $P2_1/m$, *a* = 9.2714(2), *b* = 6.7055(2), *c* = 9.6182(2) Å; β= 97.689(2)°; *V* = 592.58(3) Å^3; *Z* = 2; T = 100(2) K; μ = 0.089 mm^{-1}. Of 29178 reflections measured to 2θ 61°, 1949 were independent (R_{int} = 0.0265). Final *R*1 = 0.0363 ($I > 2\sigma$ (*I*)), *wR*2 = 0.1103 (all data).
Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic data Centre as supplementary publication no. CCDC- 773164. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

CONCLUSIONS

Using 1,1-carbonyldiimidazole (CDI) as a reagent, two synthetic routes to (1) were developed using as intermediates the 1,2,4-oxadiazoles (2) and (3).

REFERENCES

1. (a) Luthman, K.; Borg, S.; Hacksell, O. *Methods Mol. Med.* **1999**, *23*, 1. (b) Andersen, K. E.; Jorgensen, A. S.; Braestrup, C. *Eur. J. Med. Chem.* **1994**, *29*, 393.
2. Clapp, L. B. *Adv. Heterocycl. Chem.* **1976**, *65*.
3. Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenborg, H. E.; Wadsworth, H. J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726.
4. Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282
5. Carrol, F. I.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1993**, *36*, 2886.
6. Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. *J. Med. Chem.* **1994**, *37*, 2421.
7. Ankersen, M.; Peschke, B.; Hansen, B. S.; Hansen, T. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1293.
8. Cheng, C.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 3738.

9. (a) Buchanan, J. L.; Vu, C. B.; Ferry, T. J.; Corpuz, E. G.; Pradeepan, S. G.; Mani, U. N.; Yang, M.; Plake, H. R.; Varkhedkar, V. M.; Lynch, B. A.; MacNeil, I. A.; Loiacono, K. A.; Tiong, C. L.; Holt, D. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2359. (b) Vu, C. B.; Corpuz, E. G.; Merry, T. J.; Pradeepan, S. G.; Bartlett, C.; Bohacek, R. S.; Botfield, M. C.; Eyermann, D. J.; Lynch, B. A.; MacNeil, I. A.; Ram, M. K.; van Schravendijk, M. R.; Violette, S.; Sawyer, T. K. *J. Med. Chem.* **1999**, *42*, 4088. (c) Leite, A. C. L.; Vieira, R. F.; de Faria, A. R.; Wanderley, A. G.; Afiatpour, P.; Ximenes, E. C. P. A.; Srivastava, R. M.; de Oliveira, C. F.; Medeiros, M. V.; Antunes, E.; Brondani, D. J. *Il Farmaco* **2000**, *55*, 719
10. Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F.-U. *J. Med. Chem.* **2001**, *44*, 619.
11. Ohmoto, K.; Yamamoto, T.; Horiuchi, T.; Imanishi, H.; Odakagi, Y.; Kawabata, K.; Sekioka, T.; Hirota, Y.; Matsuoka, S.; Nakai, H.; Toda, M. *J. Med. Chem.* **2000**, *43*, 4927.
12. Rice, K. D.; Nuss, J. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 753.
13. Sams, C. K.; Lau, J. *Tetrahedron Lett.* **1999**, *40*, 9359.
14. (a) Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csöregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112. (b) Borg, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. *J. Med. Chem.* **1999**, *42*, 4331. (c) Liang, G.-B.; Qian, X. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2101.
15. Bedford, C. D.; Howd, R. A.; Dailey, O. D.; Miller, A.; Nolen, H. W.; Kenley, R. A.; Kern, J. R.; Winterle, J. S. *J. Med. Chem.* **1986**, *29*, 2174.
16. (a) Liang, G.-B.; Feng, D. D. *Tetrahedron Lett.* **1996**, *37*, 6627. (b) Deegan, T. L.; Nitz, T. J.; Cebzanov, D.; Porco, J. A. Jr. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 209.
17. Young, J. R.; DeVita, R. J. *Tetrahedron Lett.* **1998**, *39*, 3931.
18. De Melo, S. J.; Sobral, A. D.; de Lima Lopes, H.; Srivastava, R. M. *J. Braz. Chem. Soc.* **1998**, *9*, 465.
19. Hébert, N.; Hannah, A. L.; Sutton, S. C. *Tetrahedron Lett.* **1999**, *40*, 8547.
20. Poulain, R. F.; Tartar, A. L.; Déprez, B. P. *Tetrahedron Lett.* **2001**, *42*, 1495.
21. A. P. Melissaris, M. H. Litt *J. Org. Chem.*, **1992**, *57* (25), pp 6998–6999.
22. K. Okuma, O. Sakai, and K. Shioji*, Bull. Chem. Soc. Jpn*.,2003, *76*, 1675–1676.
23. G.M. Sheldrick, *Acta Cryst.* 2008, *A64*, 112-122.