Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Fluorine Chemistry 121 (2003) 171–175
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

Synthesis of novel fluorobenzofuroxans by oxidation of anilines and thermal cyclization of arylazides

Socorro Leyva*, Víctor Castanedo, Elisa Leyva

Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, Av. Dr. Manuel Nava No. 6, Zona Universitaria, San Luis Potosí, S.L.P 78210, Mexico

Received 31 October 2002; received in revised form 28 December 2002; accepted 2 January 2003

Abstract

The synthesis of several fluorobenzofuroxans by oxidation of fluoroanilines and thermal cyclization of fluoroarylazides is presented. The fluorobenzofuroxans prepared in this study presented tautomerism as evidenced by their NMR data. Benzofuroxans in general have biological activity and are synthetic intermediates for the preparation of several compounds with important pharmaceutical applications.

Keywords: Synthesis; Fluorobenzofuroxans; Pharmaceuticals

1. Introduction

Nitric oxide (NO) is generated in vivo and has a large number of important physiological roles in biological systems as varied as the transmission of nerve impulses [1], regulation of blood flow [2], and non-specific immune response to bacterial infection [3]. In view of NO physiological significance and transient physicochemical properties, much attention has been given to the preparation of compounds that could serve as NO donors with well-controlled releasing properties under physiological conditions [4]. Furoxans and benzofuroxans represent a recently discovered class of thiol-dependent NO donors [5]. The property of these compounds to serve as an NO donor is highly dependent on the nature, as well as the position of the substituents at the ring. In general, electron-withdrawing groups enhance the thiol-induced NO release [6].

A wide range of biological activity has been claimed for benzofuroxan and derivatives [7–10]. Some are depressants of the central nervous system, muscle-relaxants and anticonvulsants. Others present nematocidal, antimicrobial, fungicidal, herbicidal and algicidal properties. Nitrobenzofuroxans, pyridofuroxans and fused benzofuroxans have been found to inhibit nucleic acid and protein synthesis in leukemia and other forms of cancer cells.

Benzofuroxans have been reported to serve as intermediates in the synthesis of a large number of commercially available pharmaceuticals and veterinary medical products such as benzimidazole-3-oxides [7]. They react very easily with carbonyl compounds in basic media to give quinoxaline-1,4-dioxides with strong antibacterial activity [11–15]. The pyrimidine series of benzofuroxan have been prepared and studied [16,17]. In another report, quinoxaline-1,4-dioxides have been synthesized from benzofuroxans to investigate their antibacterial potency [18].

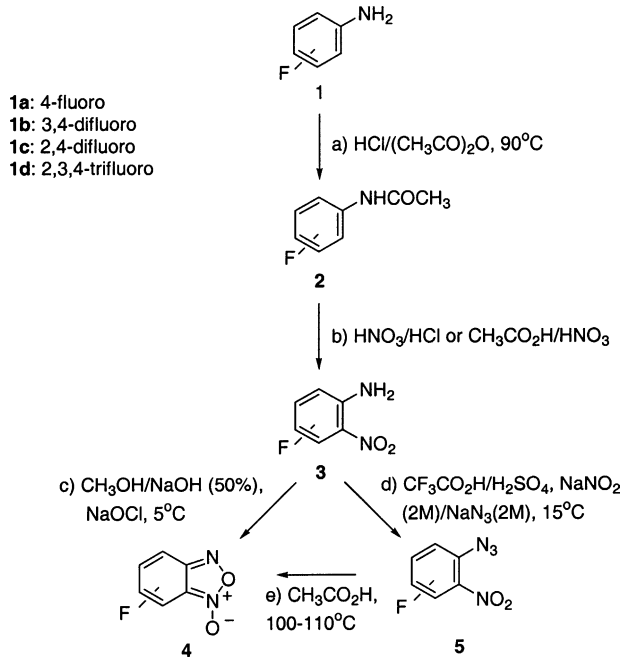
2. Results and discussion

Scheme 1 illustrates the sequence of reactions followed. In the first reaction, a commercially available fluoroaniline (**1a–1d**) was reacted with acetic anhydride in hydrochloric acid followed by a buffer solution of sodium acetate, to give the corresponding fluoroacetanilide (**2a–2d**). In the second reaction, the acetanilide (**2a–2d**) was converted to the nitroaniline (**3a–3d**) using a mixture of glacial acetic acid or hydrochloric acid and nitric acid. To induce the oxidation, a nitroaniline was dissolved in a basic alcoholic solution, cooled to 5 °C and reacted with sodium hypochlorite to produce the corresponding fluorobenzofuroxan (**4a–4d**). This oxidative cyclization is thought to occur through a single nitrene intermediate [19].

For the preparation of an arylazide **(5a–5d)**, a nitroaniline was dissolved in a solution of trifluoroacetic acid and

* Corresponding author. Tel.: +52-444-826-2440; fax: +52-44-826-2372.
E-mail address: sleyva@uaslp.mx (S. Leyva).

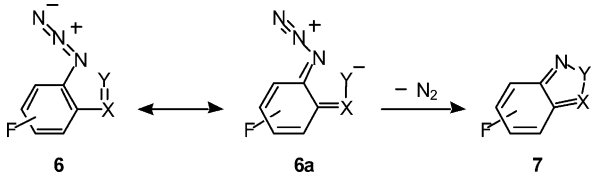
0022-1139/03/$ – see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0022-1139(03)00011-3



Scheme 1.

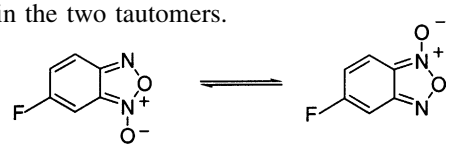
concentrated sulfuric acid (Scheme 1). The mixture was cooled to 15 °C and an aqueous solution of sodium nitrite was added dropwise maintaining the temperature to 15 °C to give a benzenediazonium salt, the resulting mixture was reacted with sodium azide to produce a fluorophenylazide. To induce thermal cyclization, an azide was dissolved in glacial acetic acid and refluxed by a period of 5–6 h. Cold water was added to the reaction mixture to form a precipitate corresponding to the fluorobenzofuroxan (**4a–4d**). This thermal cyclization could occur through a single nitrene mechanism and through an electrocyclic process, in which nitrogen is extruded and the new heterocycle (**6a**) is partly formed at the transition state (Scheme 2) [20,21]. This mechanism requires substantial coplanarity of the aromatic ring, the azido group and the *ortho*-nitro substituent. Substituents in the 3- and 6-positions of 2-nitro-arylazide slow this reaction due to steric interference with the planar cyclic transition state [22].

Benzofuroxan tautomerism has been reported in several articles [23]. This isomerization process occurs through an *ortho*-dinitrosobenzene intermediate [24–26]. In a recent study, this process was studied by multinuclear NMR methods [27]. The several fluorobenzofuroxans prepared in this study presented tautomerism. The ^{1}H NMR for 6-fluorobenzofuroxan gives three signals (7.47, 7.15 and 7.08 ppm)



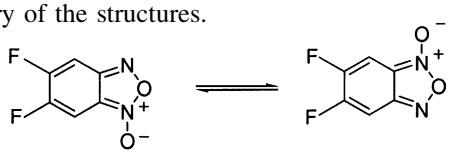
Scheme 2.

indicating the presence of three different kind of aromatic hydrogens. These signals are broad due to rapid interconversion of two tautomeric structures (**4a**, **4a'**). In agreement with these results, two broad signals (−105.52 and −102.52 ppm) are observed for the two fluorine atoms present in the two tautomers.



4a **4a'**

The ^{1}H NMR for 5,6-difluorobenzofuroxan gives two signals located at 6.67 and 6.43 ppm for the aromatic hydrogens. In this case, these signals are also broad due to rapid interconversion between **4b** and **4b'**. As expected for two tautomeric structures, two broad signals (−119.86 and –116.58 ppm) are observed in the ^{19}F NMR due to the symmetry of the structures.



4b **4b'**

The ^{1}H NMR of 4,6-difluorobenzofuroxan is more complex with four signals for the two aromatic protons. In this case, the signals are sharp and coupled to neighboring fluoro-atoms, indicating the equilibrium between the two tautomers (**4c**, **4c'**) to be a slower process. The proton located between two fluoro-atoms gives two signals at 7.96 ppm (m) and 7.87 ppm (m). The proton next to one fluoro-atom gives two signals at 7.56 ppm (dd) and 7.47 ppm (dd). In addition, the ^{19}F NMR gives four sharp signals located at −117.86, −117.43, −104.97 and −104.53 ppm.

4c **4c'**

In the case of 4,5,6-trifluorobenzofuroxan, the two tautomeric structures (**4d**, **4d'**) are also in slow equilibrium allowing for the two hydrogens to be detected. The ^{1}H NMR for this compound gives one signal at 7.93 ppm (dd) and another signal at 7.90 ppm (dd). The ^{19}F NMR gives six sharp signals located at −156.38 (m), −156.05 (m), −137.59 (d), −135.09 (d), −129.68 (dd) and −128.82 ppm (dd).

4d **4d'**

3. Conclusions

In general, aniline oxidation (98–70%) gave better benzofuroxan yields than arylazide thermal cyclization (80–40%). Thermolysis of 4-fluoro-2-nitroarylazide to benzofuroxan gave 80% yield indicating that electron-withdrawing substituents in the 4-position favor this process. Increasing the amount of fluorine atoms in the nitroarylazide reduced the benzofuroxan yields considerably and some tar was formed. This is probably due to a rapid polymerization of the singlet arylnitrene produced under photolysis or thermolysis conditions [28]. In the case of 4,6-difluoro-2-nitrophenylazide and 4,5,6-trifluoro-2-nitrophenylazide, the presence of a fluorine atom in the 6-position on the aromatic ring, *ortho* to azide, do not inhibit the benzofuroxan formation. However, our experimental results suggest the presence of this fluoro-atom to slow down the equilibrium between the two fluoro-substituted benzofuroxan tautomers.

4. Experimental

4.1. General methods

All the melting points were measured with a Fisher Johns apparatus. IR spectra were recorded on a Nicolet 205 FT–IR. UV-Vis spectra were determined on a Shimadzu UV-2401 PC. NMR spectra were recorded on a Bruker 400 MHz ARX with a QNP probe. ^{1}H NMR spectra were recorded in ppm from tetramethylsilane and ^{19}F NMR spectra were recorded in ppm from 1% Freon 113 in deuterated benzene as an external reference. Mass spectra and exact masses were obtained on a VG 70-2505 MS instrument.

4.1.1. Preparation of fluoronitroanilines

The fluoroaniline **1a–1d** (17.99–13.59 mmol) was added to 34 ml of water and 1.1 ml of concentrated hydrochloric acid. After the mixture was heated at 90 °C for 10 min, acetic anhydride (4 ml, 42.39 mmol) was added. Then, a buffer solution of sodium acetate (24.38 mmol in 6 ml of distillated water) was added, yielding the corresponding fluoroacetanilide **2a–2d**. This compound (14.80 mmol) was dissolved in 10 ml of glacial acetic acid and cooled in an ice bath, and nitric acid (7 ml) was added dropwise. After the addition of the acid, the reaction mixture was heated at 90 °C for 4 h, and was extracted with ethyl acetate. The organic phase was washed with water and concentrated to give a product. It was purified through a silica gel column using hexane as solvent to yield the corresponding aromatic amine **3a–3d**.

4.1.2. Preparation of benzofuroxans by oxidation

The fluoronitroaniline **3a–3d** (0.93 mmol) was dissolved in 10 ml of methanol combined with 1.5 ml of sodium hydroxide at 50%. Then, the mixture was cooled to 5 °C and a solution of sodium hypochlorite (6 ml, 4%) was added dropwise with vigorous stirring to give the corresponding fluorobenzofuroxan **4a–4d** as a solid. This solid was recrystallized from benzene.

4.1.3. Preparation of fluoronitroarylazides

The fluoronitrophenylazides **5a–5d** were prepared from the corresponding fluoroanilines **3a–3d** following the procedure described by Smith and Brown [29] with only minor modifications as previously described [30].

4.1.4. Preparation of benzofuroxans by thermal decomposition

The fluorophenylazide (1.65 mmol) was dissolved in 10 ml of glacial acetic acid and the solution was refluxed for 6 h. Then, the reaction mixture was poured in 100 ml of cold water and the precipitated formed was filtered under vacuum and dried to give the corresponding fluorobenzofuroxan **4a–4d** as a solid. This solid was recrystallized from benzene. Only the 4-fluoro-benzofuroxan (**4a**) was obtained with 80% yield, the other fluoro-substituted benzofuroxans (**4b–4d**) were obtained with 40% yield.

4.1.5. 4-Fluoro-2-nitroaniline *3a*

Red solid; yield 54%; mp 90–92 °C; IR (KBr, cm^{-1}): 3550–3250 (N–H), 3200 (N–H overtone), 1550–1450 (N=O); ^{1}H NMR ($CDCl_3$) δ ppm: 7.83 (1H, dd, $J_{HFortho} = 9.03$ Hz, $J_{HHmeta} = 2.91$ Hz, aromatic H), 7.18 (1H, m, aromatic H), 6.18 (IH, dd, $J_{HHortho} = 9.13$ Hz, $J_{HFmeta} = 4.59$ Hz, aromatic H), 5.80 (2H, br, amino H); ^{19}F NMR ($CDCl_3$) δ ppm: −126.48 (1F, s, aromatic F).

4.1.6. 6-Fluorobenzofuroxan *4a* prepared by oxidation

Green solid; yield 98%; mp 40–42 °C; IR (KBr, cm^{-1}): 1637 (C=N^{+}–O^{-}), 1550–1465 (doublet due to O–N^{+}–O^{-}), 1315 (N–O), 1020 and 865–760 (furoxan ring); ^{1}H NMR ($CDCl_3$) δ ppm: 7.47 (1H, br, aromatic H), 7.15 (1H, br, aromatic H), 7.08 (IH, br, aromatic H); ^{19}F NMR ($CDCl_3$) δ ppm: −105.52 (1F, s, aromatic F), −102.52 (1F, s, aromatic F); EIMS (70 eV) *m/z*: 154 (100%) [M^{+}], 138 (6%) [M^{+}–O], 124 (5%) [M^{+}–NO], 96 (19%) [M^{+}–CNO_2], 94 (24%) [M^{+}–N_2O_2]; exact mass for $C_6H_3FN_2O_2$ 154.0179, observed: 154.0181.

4.1.7. 4,5-Difluoro-2-nitroaniline *3b*

Yellow solid; yield 24%; mp 128 °C; IR (KBr, cm^{-1}): 3500–3250 (N–H), 3200 (N–H overtone), 1550–1450 (N=O); ^{1}H NMR ($CDCl_3$) δ ppm: 8.00 (1H, dd, $J_{HFortho} = 10.50$ Hz, $J_{HFmeta} = 8.20$ Hz, aromatic H), 6.60 (1H, dd, $J_{HFortho} = 11.19$ Hz, $J_{HFmeta} = 6.67$ Hz, aromatic H), 6.10 (2H, br, amino H); ^{19}F NMR ($CDCl_3$) δ ppm: −148.94 (1F, d, $J_{FF} = 11.29$ Hz, aromatic F), −124.31 (1F, d, $J_{FF} = 11.29$ Hz, aromatic F).

4.1.8. 5,6-Difluorobenzofuroxan *4b* prepared by oxidation

Yellow solid; yield 81%; mp 140–147 °C; IR (KBr, cm^{-1}): 1637 (C=N^{+}–O^{-}), 1550–1465 (doublet due to

O–N^+–O^-), 1342 (N–O), 954 and 865–760 (furoxan ring); ^{1}H NMR ($CDCl_3$) δ ppm: 6.67 (1H, br, aromatic H), 6.43 (1H, br, aromatic H); ^{19}F NMR ($CDCl_3$) δ ppm: −119.86 (1F, s, aromatic F), −116.58 (1F, s, aromatic F); EIMS (70 eV) *m/z*: 172 (8%) [M^+], 136 (57%) [M^+–HOF], 121 (17%) [M^+–$N_2O_2F + C_2H_4$], 113 (20%) [M^+–N_2O_2 + H], 93 (34%) [M^+–N_2O_2F], 92 (5%) [M^+–HN_2O_2F]; exact mass for $C_6H_2F_2N_2O_2$ 172.0084, observed: 172.0109.

4.1.9. 4,6-Difluoro-2-nitroaniline ***3c***

Yellow solid; yield 14%; mp 57–60 °C; IR (KBr, cm^{-1}): 3500–3300 (N–H), 1534–1438 (N=O); ^{1}H NMR ($CDCl_3$) δ ppm: 7.70 (1H, br, aromatic H), 7.11 (1H, br, aromatic H), 6.00 (2H, br, amino H); ^{19}F NMR ($CDCl_3$) δ ppm: −128.48 (1F, s, aromatic F), −125.38 (1F, s, aromatic F).

4.1.10. 4,6-Difluorobenzofuroxan ***4c*** *prepared by oxidation*

Yellow solid; yield 80%; mp 140–142 °C; IR (KBr, cm^{-1}): 1648 (C=N^+–O^-), 1550–1465 (doublet due to O–N^+–O^-), 1342 (N–O), 995 and 865–760 (furoxan ring); ^{1}H NMR (CD_3COCD_3) δ ppm: 7.96 (1H, m, aromatic H), 7.87 (1H, m, aromatic H), 7.56 (1H, dd, aromatic H), 7.47 (1H, dd, aromatic H); ^{19}F NMR (CD_3COCD_3) δ ppm: −117.86 (1F, s, aromatic F), −117.43 (1F, s, aromatic F), −104.97 (1F, s, aromatic F), −104.53 (1F, s, aromatic F); EIMS (70 eV) *m/z*: 172 (8%) [M^+], 171 (43%) [M^+–H], 170 (54%) [M^+–H_2], 156 (13%) [M^+–O], 154 (75%) [M^+–F + H], 153 (13%) [M^+–F], 152 (11%) [M^+–HF], [M^+–HF], 151 (17%) [M^+–H_2F], 142 (100%) [M^+–NO]; exact mass for $C_6H_2F_2N_2O_2$ 172.0084, observed: 172.0110.

4.1.11. 4,5,6-Trifluoro-2-nitroaniline ***3d***

Yellow solid; yield 10%; mp 44–47 °C; IR (KBr, cm^{-1}): 3525–3250 (N–H), 3200 (N–H overtone), 1534–1398 (N=O); ^{1}H NMR ($CDCl_3$) δ ppm: 7.86 (1H, m, aromatic H), 6.12 (2H, br, amino H); ^{19}F NMR ($CDCl_3$) δ ppm: −153.04 (1F, d, J_{FF} = 9.41 Hz, aromatic F), −148.67 (1F, d, J_{FF} = 11.29 Hz, aromatic F), −147.71 (1F, dd, J_{FF} = 11.29 Hz, J_{FF} = 9.41 Hz, aromatic F).

4.1.12. 4,5,6-Trifluorobenzofuroxan ***4d*** *prepared by oxidation*

Yellow solid; yield 70%; mp 61–63 °C; IR (KBr, cm^{-1}): 1637 (C=N^+–O^-), 1550–1465 (doublet due to O–N^+–O^-), 1018 and 865–760 (furoxan ring); ^{1}H NMR ($CDCl_3$) δ ppm: 7.93 (1H, dd, aromatic H), 7.90 (1H, dd, aromatic H); ^{19}F NMR ($CDCl_3$) δ ppm: −156.38 (1F, m, aromatic F), −156.05 (1F, t, aromatic F), −137.59 (1F, d, aromatic F), −135.09 (1F, d, aromatic F), −129.68 (1F, dd, aromatic F), −128.82 (1F, dd, aromatic F); EIMS (70 eV) *m/z*: 190 (3%) [M^+], 191 (16%) [M^+ + H], 174 (5%) [M^+–O], 171 (27%) [M^+–F], 170 (7%) [M^+–HF], 160 (68%) [M^+–NO], 159 (95%) [M^+–HNO]; exact mass for $C_6H_3F_3N_2O_2$ 189.9901, observed: 190.0109.

4.1.13. 4-Fluoro-2-nitrophenylazide ***5a***

Red solid; yield 85%; mp 30–31 °C; IR (KBr, cm^{-1}): 2125 (azide group), 1540 and 1275 (N=O).

4.1.14. 4,5-Difluoro-2-nitrophenylazide ***5b***

Red solid; yield 58%; mp 25–28 °C; IR (KBr, cm^{-1}): 2125 (azide group), 1540 and 1275 (N=O).

4.1.15. 4,6-Difluoro-2-nitrophenylazide ***5c***

Red oil; yield 40%; IR (KBr, cm^{-1}): 2125 (azide group), 1540 and 1275 (N=O).

4.1.16. 4,5,6-Trifluoro-2-nitrophenylazide ***5d***

Yellow oil, yield 60%; IR (KBr, cm^{-1}): 2125 (azide group).

Acknowledgements

Financial support by Miguel Hidalgo—CONACyT CB06, CONACyT (Grant 485100-5-32225-E) and UASLP (C98-FAI-06-8.44) is gratefully acknowledged. We thank Prof. Miguel García-Garibay from the University of California at Los Angeles for help with the NMR and MS measurements.

References

[1] J.F. Kerwin Jr., J.R. Lancaster Jr., P.L. Feldman, J. Med. Chem. 38 (1995) 4343.
[2] J.S. Stamler, Nature 380 (1996) 221.
[3] J.T. Groves, S.S. Marla, J. Am. Chem. Soc. 117 (1995) 9578.
[4] J.E. Saavedra, T.R. Billiar, D.L. Williams, Y.M. Kim, S.C. Watkins, L.K. Keefer, J. Med. Chem. 40 (1997) 1947.
[5] A. Gasco, R. Fruttero, G. Sorba II, Farmaco 51 (1996) 617.
[6] C. Medana, A. Di Stilo, S. Visentin, R. Fruttero, D. Ghigo, A. Bosia, Pharm. Res. 16 (1999) 956.
[7] A. Gasco, A.J. Boulton, Adv. Heterocycl. Chem. 29 (1981) 251.
[8] P.B. Ghosh, B.J. Everitt, J. Med. Chem. 17 (1974) 203.
[9] P.B. Ghosh, B. Ternai, M.W. Whitehouse, Med. Res. Rev. 2 (1981) 158.
[10] P.B. Ghosh, M.W. Whitehouse, J. Med. Chem. 12 (1969) 505.
[11] C.H. Issidorides, M.J. Haddadin, J. Org. Chem. 31 (1966) 4067.
[12] A. Monge, J.A. Palop, J.C. Del Castillo, J. Heterocycl. Chem. 31 (1994) 33.
[13] D.L. Terrian, M.A. Houghtaling, J.R. Ames, J. Chem. Educ. 69 (1992) 589.
[14] T. Takabatake, Y. Hasegawa, M.J. Hasegawa, Heterocycl. Chem. 30 (1993) 1477.
[15] A. Monge, J.A. Palop, J.C. Del Castillo, J.M. Calderó, J. Roca, G. Romero, J. Del Río, B. Lasheras, J. Med. Chem. 36 (1993) 2745.
[16] M. Sako, S. Oda, S. Ohara, K. Hirota, Y. Maki, J. Org. Chem. 63 (1998) 6947.
[17] F. Yoneda, Y. Sakuma, M. Ueno, J. Heterocycl. Chem. 10 (1973) 415.
[18] M.M. El-Abadelah, M.Z. Nazer, N.S. El-Abadla, H. Meier, Heterocycles 41 (1995) 2203.
[19] L.K. Dyall, Aust. J. Chem. 37 (1984) 2013.
[20] N.J. Dickson, L.K. Dyall, Aust. J. Chem. 33 (1980) 91.
[21] L.K. Dyall, Aust. J. Chem. 39 (1986) 89.

[22] M. Chaykovsky, H.G. Adolph, J. Heterocycl. Chem. 28 (1991) 1491.
[23] A.R. Katritzky, M.F. Gordeev, Heterocycles 35 (1993) 483.
[24] S. Murata, H. Tomioka, Chem. Lett. (1992) 57.
[25] I.R. Dunkin, M.A. Lynch, A.J. Boulton, N. Henderson, J. Chem. Soc. Chem. Commun. (1991) 1178.
[26] N.P. Hacker, J. Org. Chem. 56 (1991) 5216.
[27] P. Cmoch, W. Schilf, Magn. Reson. Chem. 37 (1999) 758.
[28] E. Leyva, R. Sagredo, Tetrahedron 54 (1998) 7367.
[29] P.A.S. Smith, B.B. Brown, J. Am. Chem. Soc. 73 (1951) 2438.
[30] E. Leyva, D. Munoz, M.S. Platz, J. Org. Chem. 54 (1989) 5938.