Novel synthesis of 1-alkyl-4-tosyl-3-carboxymethyl-1,2,3,4-tetrahydroquinoxalin-2-ones

Norma F. Santos-Sánchez[a,*], Raúl Salas-Coronado[a], Raúl Colorado-Peralta[b], Adrián Peña-Hueso[b], Sonia A. Sánchez-Ruiz[b], and Angelina Flores-Parra[b,*]

[a]Instituto de Agroindustrias, Universidad Tecnológica de la Mixteca, Huajuapan de León, Oaxaca, Carretera a Acatlima km 2.5, 69000 México
[b]Department of Chemistry, Cinvestav Mexico. A. P. 14-740, 07000 México, D.F.
E-mail: nsantos@mixteco.utm.mx, aflores@cinvestav.mx

Dedicated to Professor Rosalinda Contreras

Abstract

1-Alkyl-4-tosyl-3-carboxymethyl-1,2,3,4-tetrahydroquinoxalin-2-ones were synthesized by means of a key step that consisted in a condensation reaction between *o*-phenylenediamine and maleic anhydride, followed by tosylation and final alkylation. The X-ray diffraction of 3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one benzyl ester (**1e**) and 1-benzyl-3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one benzyl ester (**1f**) is reported.

Keywords: 1-Alkyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-ones, cyclization, tosylation, phase transfer catalysis

Introduction

Quinoxalin-2-ones display interesting biological properties, including the inhibition of the aldose reductase enzyme,[1] partial agonists for complex receptors *γ*-aminobutyric acid (GABA)/benzodiazepine[2] and as multiple-drug-resistance antagonists,[3] amongst others. Additionally, the quinoxalin-2-one, Figure 1, has been used as an intermediate in the preparation of diverse derivatives with antimicrobial,[4] antifungi,[5] antiviral[6] and anticancer[7] activity.

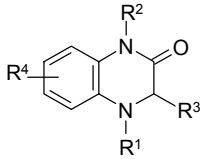
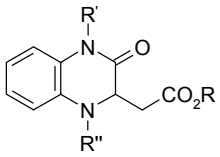


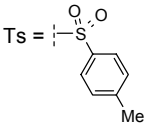
Figure 1. 1,2,3,4-Tetrahydroquinoxalin-2-one.

 ©ARKAT USA, Inc.

Herein, we report a novel synthetic route to a series of novel compounds 1-alkyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one with CH_2CO_2R group in position 3 (**1a-i**), Figure 2.



1a R = R' = R" = H
1b R = R' = H, R" = Ts
1c R = Me, R' = H, R" =Ts
1d R = R' = Me, R" = Ts
1e R = Bn, R' = H, R" = Ts
1f R = R' = Bn, R" = Ts
1g R = CH_2OEt, R' = H, R" = Ts
1h R = R' = CH_2OEt, R" = Ts
1i R = R' = Pre, R" = Ts



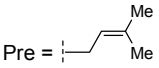
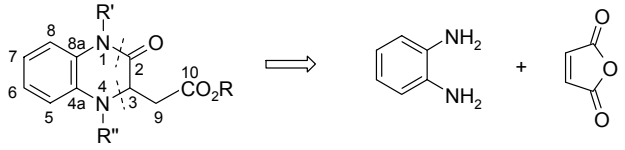


Figure 2. Compounds reported.

The key step of this route involves the condensation of *o*-phenylenediamine (**2**) with maleic anhydride (**3**) that leads directly to the basic backbone, Scheme 1. The quinoxalin-2-ones **1** have groups CH_2CO_2R (R = H, alkyl), in position 3, and were functionalized in N1 and N4 positions. The tosyl group in N4 has been shown to be responsible for the inhibition of the aldose reductase enzyme, *in vitro* and *in vivo*,[1] whereas the substituent in N1 modifies the solubility of the molecule.



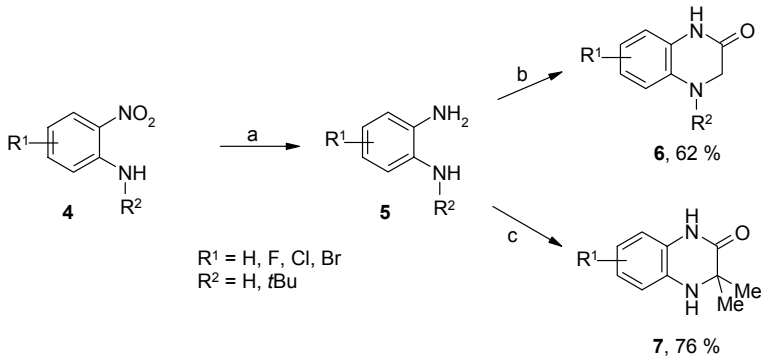
1 **2** **3**

Scheme 1. Retrosynthesis for the preparation of 1,2,3,4-tetrahydroquinoxalin-2-one.

Results and Discussion

Typical syntheses of 1,2,3,4-tetrahydroquinoxalin-2-ones involve two or more reaction steps.[1-6, 9-11] The most common synthesis of these molecules is the cyclization of *o*-phenylenediamine, or substituted derivative, with an α-haloester under basic conditions. However, this route involves at least three steps giving moderate yields, Scheme 2.[2a-b,] In another reported methods, the

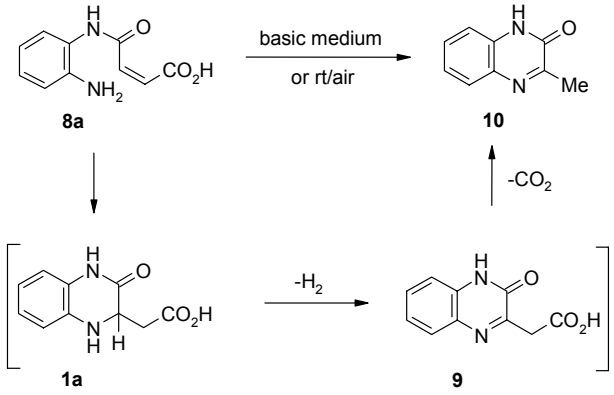
quinoxalinones has been prepared in solution[2a, 10a] and on solid support[9, 10b] from α-amino acid esters and 2-fluoronitrobenzenes.



Reagents: (a) H_2, Pd/C; (b) XCH_2CO_2Et, $EtN(iPr)_2$/THF; (c) Ethyl 2-bromoisobutirate, $EtN(iPr)_2$/DMF

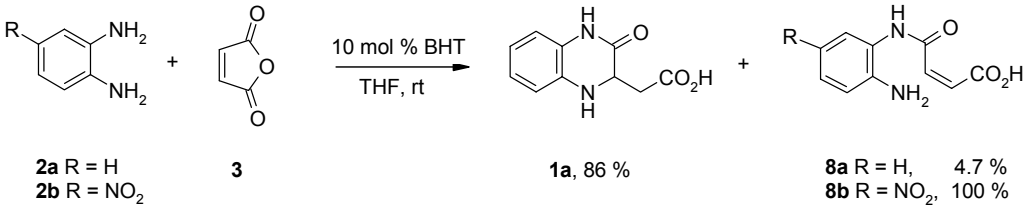
Scheme 2. 1,2,3,4-tetrahydroquinoxalin-2-ones from the *N*-alkyl phenylenediamines.[2a-b]

Thus, we decide to look for a convenient synthesis of tosylated compounds **1b-i**, through the condensation reaction of *o*-phenylenediamine (**2a**) with the maleic anhydride (**3**). When the condensation of *o*-phenylenediamine with maleic anhydride was carried out at room temperature in THF, the expected compound **1a** was not obtained, instead the (*Z*)-3-(2-aminophenylcarbamoyl)propenoic acid (**8a**)[12] was the main reaction product (98 %). Compound **8a** is the product of a partial condensation of the reagents, when we have tried to close the ring, we noted that **8a** is unstable and under air exposure or in basic medium is rapidly transformed into the 3-methylquinoxalin-2-one (**10**). This observation was important because, it implies the formation of two intermediates (**1a** and **9**), Scheme 3. We have observed that after 6 h in refluxing THF and in N_2 atmosphere, the acid **8a** was partially transformed into the 1,2,3,4-tetrahydroquinoxalin-2-one **1a**.



Scheme 3. Proposed mechanism for the transformation of (*Z*)-3-(2-aminophenylcarbamoyl) propenoic acid (**8a**) into 1,2-dihydroquinoxalin-2-one (**10**).

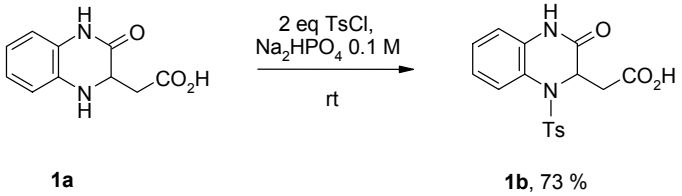
Due to the fact that compound **1a** in our previous attempts was obtained in low yield, we used a catalyst in order to promote the cyclization and to prevent oxidation-decarboxylation, and therefore an antioxidant (butylated hydroxytoluene BHT) was incorporated into the reaction. The decomposition of **1a** into **10** was avoided and the yield was improved (86 %, after crystallization), while only 4.7 % of acid **8a** was formed, Scheme 4. When the 4-nitro-1,2-phenylenediamine (**2b**) react with maleic anhydride, the (*Z*)-3-(2'-amino-5'-nitrophenylcarbamoyl)propenoic acid (**8b**) was obtained in 100 %. It is important to indicate that the reaction of maleic anhydride with 4-substitued *o*-phenylenediamines (e.g. 4-Cl or 4-OMe) gave a mixture of not identified products.



Scheme 4. Cyclization reaction of *o*-phenylenediamines with maleic anhydride.

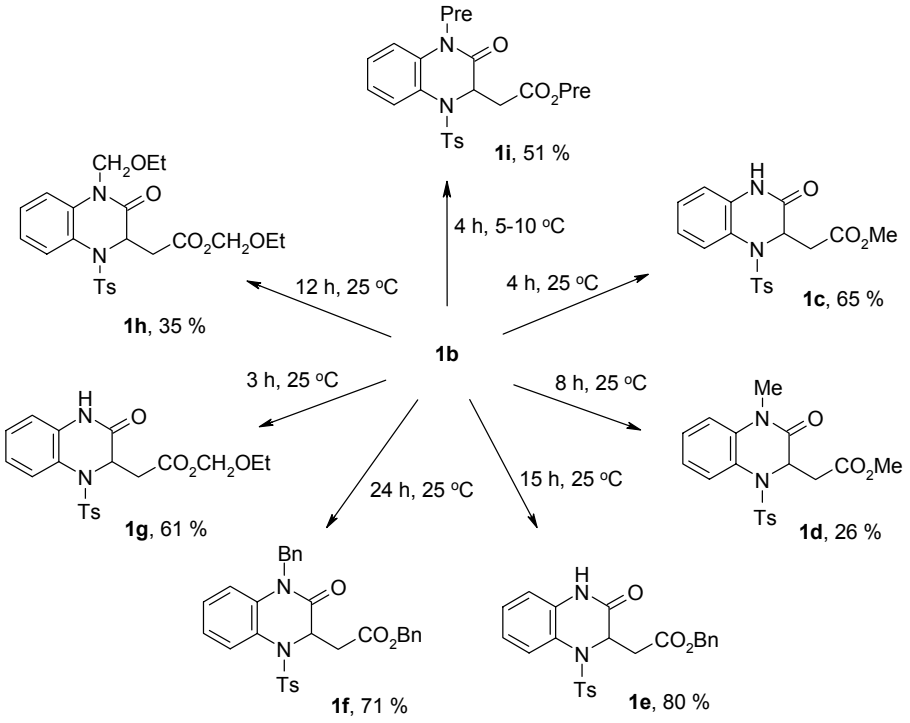
Once the quinoxalin-2-one **1a** was obtained, it turns out to be relatively stable and easy to purify. Nevertheless, it is important to indicate that when **1a** is either directly exposed to the air or dissolved in a basic medium, it is transformed into the oxidized compound **10**. This situation makes difficult the subsequent selective protection of N1 and/or N4, because these reactions are generally carried out in basic medium.

The reported basic conditions for tosylation of 1,2,3,4-tetrahydroquinoxalin-2-ones[1] (suspension of Na_2CO_3 and tosylchloride in acetone under N_2 atmosphere and 18 h of reaction) were inappropriate for **1a**, due to decomposition. For this reason, we developed a novel tosylation procedure that consisted in controlling the pH (5.5) of the reaction medium using a buffer dibasic sodium phosphate solution [0.1 M], Scheme 5. The 3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one (**1b**) precipitated from the reaction mixture and was obtained in 73 % yield after crystallization. The tosyl group in **1b** increases its stability allowing the N1 alkylation.



Scheme 5. Tosylation reaction of **1a** in a buffer solution.

The N1 alkylation of tetrahydroquinoxalin-2-ones with benzyl and allyl halides in the presence of 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) in DMF[13], as well as the alkylation with ethyl bromoacetate and NaH in dioxane[1] have been reported. In our research, this alkylation was performed under phase transfer catalysis conditions of compound **1b**, employing a catalytic amount of tetrabutylammonium hydrogensulphate (TBAHS). The reaction time was variable and depends on the alkyl halide reactivity and amount, Scheme 6. The esters **1c**, **1e** and **1g** were obtained in moderate to good yields and the N1 alkylation products **1d**, **1f**, **1h** and **1i** gave in low to good yields (<71 %). The formation of the esters was simply confirmed *via* the existence of the set of carbons in its ^{13}C NMR spectrum. The low yield for **1d** is probably due to "poisoning" of the phase transfer agent with methyl iodide.[14]



Scheme 6. Products resulting from phase transfer alkylation reaction of **1b**.

The structures of **1e** and **1f** were confirmed by single-crystal X-ray crystallography. A perspective view of **1e** and **1f**, together with the atom-numbering scheme, are shown to left of Figures 3 and 4, respectively. All interatomic distances can be considered normal. The side-branch conformation in C3 in **1e** and **1f** is comparable and may be explained by intramolecular C-H···N hydrogen bonds between N4 and H20. This interaction approaches the phenyl ring to atom N4.

Conformational analysis of the puckered heteroatom ring of the quinoxalinone system, in **1e** shows an intermediate conformation between screw-boat and envelope. The total puckering

amplitude is Q_T = 0.410 Å, calculated by the Cremer-Pople method.[15] Molecules of **1e** are held together by N-H···O intermolecular hydrogen bond between H1 and O2 and intermolecular C-H···O between H9 and O10b forming a six member ring, see right image shown in Figure 1.

Compound **1f** shows a screw-boat conformation. The total puckering amplitude is Q_T = 0.508 Å. The molecules of **1f** are held together by C-H···O interactions between H7 and O4, a sulphonamidic oxygen, see right image of Figure 2. The benzyl group in N1 of compound **1f** have an perpendicular orientation respect to quinoxalinone system. This is attributed to hindrance interactions.

The conformational differences between **1e** and **1f** can be attributed to benzyl substituent in N1-of **1f**.

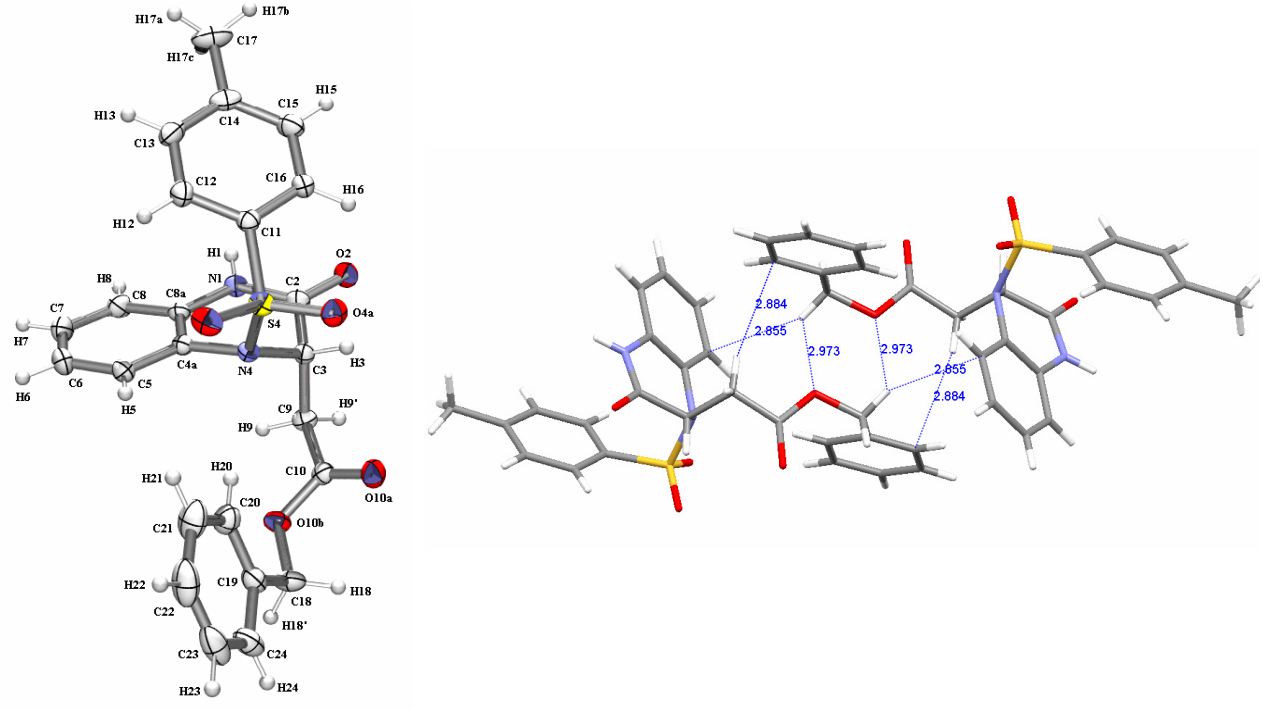


Figure 3. ORTEP drawing of X-ray structure (left) and intermolecular interactions (Å) pairs of two crystallographical independent molecules (right) of **1e**.

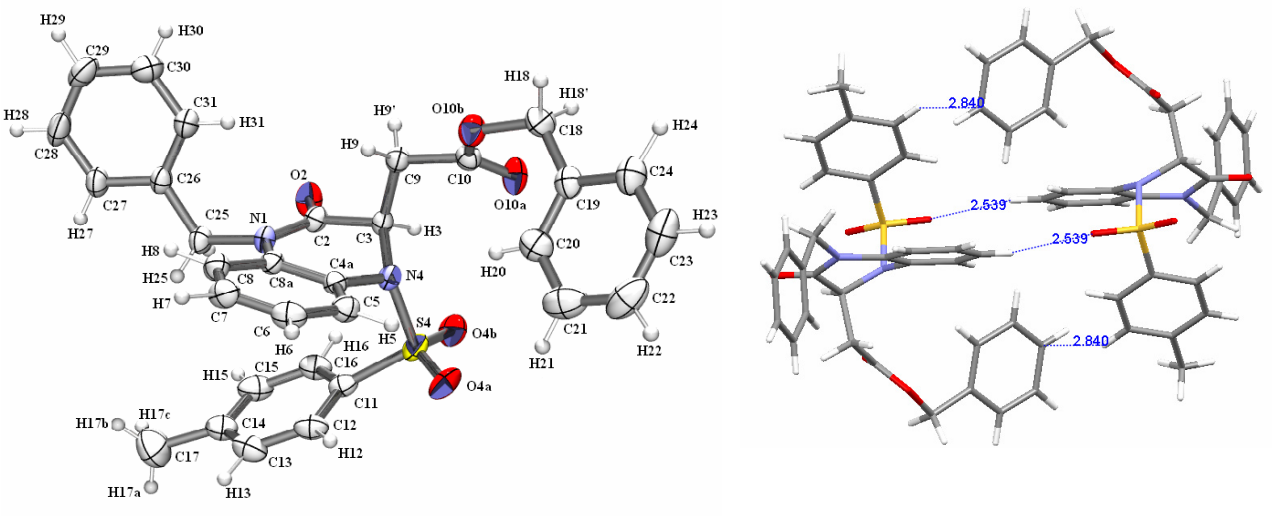


Figure 4. ORTEP drawing of X-ray structure (left) and intermolecular interactions (Å) pairs of two crystallographical independent molecules (right) of **1f**.

Conclusions

We have developed a novel approach for the synthesis of N1 and C3 substituted 4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-ones through a cyclization reaction between maleic anhydride and *o*-phenylenediamine, followed by tosylation and a subsequent alkylation reaction under a phase transfer catalysts. The newly developed methodology is general to allylic and benzylic substituents and provides quinoxalinones C3 substituted in moderate to good yields depending on the nature used in the final alkylation step.

Experimental Section

General Procedures. All commercially available chemicals were reagent grade and used without further purification. The chromatographic purification was made on flash column chromatography using silica gel (230-400 mesh, 60 Å). The melting points are uncorrected. IR spectra were obtained from a Perkin-Elmer spectrum GX instrument using KBr plates for solid samples and $CHCl_3$ solution for liquid samples. The low resolution mass spectra were obtained by direct insertion at 20 eV in a HP 5989 spectrometer. The samples were ionized electronically (EI). HRMS data were obtained in HPLC equipment coupled to MSD TOF Agilent. If not stated otherwise, the NMR spectra were measured in DMSO-d_6 using TMS as internal standard for ^{1}H and ^{13}C NMR spectroscopy. ^{1}H NMR: 400, 300, and 270 MHz spectrometers. ^{13}C NMR: 100, 67.5, and 75 MHz spectrometers. Unambiguous proton NMR assignments were established by

means of {^{1}H, ^{1}H}-COSY and {^{1}H, ^{13}C}-HETCOR experiments. For the crystallographic study of **1e** and **1f**, data were measured on a Nonius Kappa CCD instrument with area detector using graphite-monocromated Mo Kα radiation. Intensities were measured using φ + ω scans. Structures were collected at 173 and 293 K, respectively. Crystals of **1e** and **1f** were obtained from hexane/AcOEt, they are triclinic space group P-1 [a = 8.6123 (2), b = 8.9119 (2), c = 15.3079 (4)Å; α = 74.4416 (10), β = 74.9927 (10), γ = 78.6596 (11); R_1 = 0.0441; wR_2 = 0.0518 for **1e** and a = 8.6030 (2), b = 10.3101 (3), c = 16.1507 (5); α = 100.3075 (11), β = 96.7041 (11), γ = 104.8400 (12); R_1 = 0.0445; wR_2 = 0.0546 for **1f**]. In both structures, all hydrogen atoms were located and their positions were refined and solved by direct methods using SHELX-97,[16] and the refinement (based on F^2 of all data) was performed by full matrix least-squares techniques. All non-hydrogen atoms were refined anisotropically. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as numbers: 654371 (**1e**) and 654372 (**1f**). Copies of the data can be obtained, free of charge, on applications to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3-(Carboxymethyl)-1,2,3,4-tetrahydroquinoxalin-2-one (1a). To a solution of *o*-phenylenediamine (2 g, 18.5 mmol) and BHT (0.2 g, 0.9 mmol) in THF (40 mL) was added dropwise a solution of maleic anhydride (1.9 g, 19.4 mmol) in THF (40 mL) over a 0.5 h period. The mixture, with a limited exposition to air, was stirred at room temperature for 3 days. After 3 days, the supernatant was removed by filtration and washed with ethyl ether to give 0.18 g of **8a**[12] (4.7 %). The filtrate was evaporated under reduced pressure and brown residue was precipitated from acetone/hexane to afford the product **1a** (3.29 g, 86 %) as a brown solid. Mp 169-170 °C; R_f (4:6:0.1, hexane: AcOEt: formic acid) 0.36. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 12.26 (bs, 1H, CO_2H), 10.30 (bs, 1H, CONH), 6.78-6.57 (m, 4H, Ar), 5.98 (s, 1H, NH), 4.10 (t, J = 6.0 Hz, 1H, H3), 2.73 (dd, J = 16.3, 5.1 Hz, 1H, H9), 2.55 (dd, J = 16.3, 6.9 Hz, 1H, H9'); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 173.0 (s), 167.5 (s), 134.8 (s), 126.8 (d), 123.6 (d), 118.8 (d), 115.7 (d), 114.5 (d), 53.3 (d), 37.4 (t). MS [EI, *m*/*z* (%)]: 206 (100), 160 (77), 147 (96), 119 (43). HRMS calcd for $[C_{10}H_{10}N_2O_3 + Na]^+$ 229.0584, found 229.0581. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3370 (s), 3063 (b), 1706 (vs), 1434 (s).

3-Carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one (1b). To a solution of **1a** (2.66 g, 12.9 mmol) in Na_2HPO_4 0.1 M freshly prepared (266 mL) was added tosyl chloride (4.92 g, 25.8 mmol). The mixture was allowed to mix at rt for 48 h. After 48 h, the precipitated product was filtrated and washed with water. The pale pink solid was precipitated from ethanol/acetone to afford the **1b** (3.38 g, 73 %) as a beige solid. Mp 274-276 °C; R_f (4:6:0.1, hexane: AcOEt: formic acid) 0.27. ^{1}H NMR (270.17 MHz, DMSO-d_6) δ 10.40 (s, 1H, NH), 7.50 (d, J = 7.9 Hz, 1H, H5), 7.29-7.09 (m, 6H, Ar), 6.78 (d, J = 7.7 Hz, 1H, H8), 4.92 (dd, J = 10.2, 4.5 Hz, 1H, H3), 2.50 (dd, J = 15.1, 4.5 Hz, 1H, H9), 2.32 (s, 3H, Me17), 2.16 (dd, J = 15.1, 10.2 Hz, 1H, H9'); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 170.4 (s), 165.9 (s), 145.0 (s), 134.2 (s), 133.4 (s),

130.3 (d), 129.0 (d), 128.5 (d), 127.2 (d), 123.5 (d), 121.5 (bs), 116.6 (d), 56.5 (d), 36.1 (t), 21.6(q). MS [EI, *m*/*z* (%)]: 360 (20), 187 (58), 160 (100), 131 (72), 91 (63). HRMS calcd $[C_{17}H_{16}N_2O_5S + Na]^+$ 383.0672, found 383.0661. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3351 (b), 3076 (b), 1690 (vs), 1432 (s).

General procedure for 1c-i

To a solution of tetrahydroquinoxalin-2-one **1b** (0.50 g, 1.39 mmol) in CH_2Cl_2 (50 mL) were added tetrabutylammonium hydrogensulphate (TBAHS, 0.095 g, 0.28 mmol), the corresponding alkyl halide (2.22 mmol for obtain the corresponding ester **1c**, **1e** and **1g**, and 3.48 mmol for obtain the corresponding N1-alkyl ester **1d**, **1f** and **1h-i**), and 10% aq. NaOH (40 mL). The resulting mixture was stirred rapidly at room temperature. TLC analysis (silica, 1:1 hexane: AcOEt) was used to monitor the reaction progress. The layers were separated and the aqueous layer was extracted with fresh CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography on silica gel or by precipitation to afford the corresponding 3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one ester (**1c**, **1e** and **1g**) or N1-alkyl 3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one ester (**1d**, **1f** and **1h-i**).

3-Carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one methyl ester (1c). Obtained from the crude product by flash chromatography (3:2, hexane: AcOEt) like a white solid (0.34 g, 65 %). Mp 199-200 °C; R_f (1:1, hexane: AcOEt) 0.38. ^{1}H NMR (399.78 MHz, DMSO-d_6) δ 10.45 (s, 1H, NH), 7.50 (d, J = 7.9 Hz, 1H, H5), 7.28 (d, J = 8.0 Hz, 3H, H12, H16, H7), 7.21 (d, J = 8.0 Hz, 2H, H13, H15), 7.11 (t, J = 7.9 Hz, 1H, H6), 6.79 (d, J = 7.9 Hz, 1H, H8), 4.89 (dd, J = 9.9, 4.6 Hz, 1H, H3), 3.58 (s, 3H, OMe), 2.61 (dd, J = 14.9, 4.6 Hz, 1H, H9), 2.33 (s, 3H, Me17), 2.31 (dd, J = 14.9, 9.9 Hz, 1H, H9'); ^{13}C NMR δ (100.53 MHz, DMSO-d_6) δ 169.4 (s), 165.7 (s), 145.0 (bs), 134.3 (s), 133.2 (s), 130.3 (d), 128.9 (d), 128.3 (d), 127.2 (d), 123.5 (d), 121.5 (bs), 116.6 (d), 56.4 (d), 52.4 (q), 36.0 (t), 21.6 (q). MS [EI, *m*/*z* (%)]: 374 (16), 219 (71), 187 (100), 159 (97). HRMS calcd $[C_{18}H_{18}N_2O_5S + H]^+$ 375.1009, found 375.1008. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3078 (w), 2916 (w), 1741 (vs), 1691 (vs).

1-Methyl-3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one methyl ester (1d). Obtained from the crude product by flash chromatography (7:3, hexane: AcOEt) like a white solid (0.14 g, 26 %). Mp 133-134 °C; R_f (1:1, hexane: AcOEt) 0.48. ^{1}H NMR (399.78 MHz, DMSO-d_6) δ 7.50 (dd, J = 7.9, 1.5 Hz, 1H, H5), 7.41 (td, J = 7.9, 1.5 Hz, 1H, H7), 7.27 (d, J = 8.1 Hz, 2H, H12, H16), 7.24 (td, J = 7.9, 1.3 Hz, 1H, H6), 7.13 (d, J = 8.1 Hz 2H, H13, H15), 7.07 (dd, J = 7.9, 1.3 Hz, 1H, H8), 4.98 (dd, J = 10.2, 4.7 Hz, 1H, H3), 3.59 (s, 3H, CO_2*Me*), 2.62 (s, 3H, NMe), 2.61 (dd, J = 15.1, 4.7 Hz, 1H, H9), 2.32 (s, 3H, Me17), 2.26 (dd, J = 15.1, 10.2 Hz, 1H, H9'); ^{13}C NMR (100.53 MHz, DMSO-d_6) δ 169.4 (s), 164.7 (s), 145.2 (bs), 135.4 (bs), 133.4 (s), 130.1 (d), 129.6 (d), 129.1 (d), 127.1 (d), 124.3 (d), 123.1 (s), 116.6 (d), 56.8 (d), 52.5 (q), 35.5 (t), 28.9 (q), 21.5 (q). HRMS calcd $[C_{19}H_{20}N_2O_5S + H]^+$ 389.1165, found 389.1168. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3050 (m), 2961 (s), 1742 (vs), 1677 (vs), 1379 (vs).

3-Carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one benzyl ester (1e). Obtained from the crude product by flash chromatography (4:1, hexane: AcOEt) like a white solid (0.50 g, 80 %). Mp 219-220 °C; R_f (1:1, hexane: AcOEt) 0.50. ^{1}H NMR (399.78 MHz, DMSO-d_6) δ 12.78 (sa, 1H, NH), 7.59 (dd, J = 7.8, 0.6 Hz, 1H, H5), 7.57-6.91 (m, 11H, aromatics), 6.78 (d, J = 7.9 Hz, 1H, H8), 5.17 (dd, J = 10.1, 4.6 Hz, 1H, H3), 4.70 (d, J = 16.6 Hz, 1H, H18), 4.14 (d, J = 16.6 Hz, 1H, H18'), 2.65 (dd, J = 14.9, 4.6 Hz, 1H, H9), 2.38 (s, 3H, Me17), 2.31 (dd, J = 14.9, 10.1 Hz, 1H, H9'); ^{13}C NMR (100.53 MHz, DMSO-d_6) δ 170.2 (s), 165.3 (s), 145.4 (s), 136.4 (s), 134.5 (s), 133.9 (s), 130.4 (d), 129.3 (d), 129.2 (d), 128.9 (d), 127.6 (d), 127.3 (d), 126.4 (d), 124.4 (d), 123.3 (s), 116.6 (d), 56.8 (d), 45.4 (t), 36.0 (t), 21.6 (q). MS [EI, *m*/*z* (%)]: 450 (3), 295 (23), 187 (11), 91 (100). HRMS calcd $[C_{24}H_{22}N_2O_5S + H]^+$ 451.1322, found 451.1322. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3467 (b), 3078 (m), 2979 (m), 1744 (vs), 1697 (vs). The structure was confirmed by single-crystal X-ray crystallography.

1-Benzyl-3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one benzyl ester (1f). Obtained from the crude product by precipitation in hexane/AcOEt like a white solid (0.53 g, 71 %). Mp 142-145 °C; R_f (1:1, hexane: AcOEt) 0.78. ^{1}H NMR (270.17 MHz, DMSO-d_6) δ 7.61-7.14 (m, 17H, aromatics), 6.81 (bd, J = 6.7 Hz, 1H, H8), 5.21 (dd, J = 10.1, 5.0 Hz, 1H, H3), 5.19 (d, J = 12.6 Hz, 1H, H18), 5.06 (d, J = 12.6 Hz, 1H, H18'), 4.70 (bd, J = 16.5 Hz, 1H, H25), 4.21 (bd, J = 16.5 Hz, 1H, H25'), 2.86 (dd, J = 15.1, 4.7 Hz, 1H, H9), 2.49 (dd, J = 15.1, 10.1 Hz, 1H, H9'), 2.38 (s, 3H, Me17); ^{13}C NMR (67.93 MHz, DMSO-d_6) δ 168.2 (s), 164.5 (s), 144.9 (bs), 135.7(s), 135.6 (s), 133.7 (s), 130.9 (d), 129.5 (d), 128.8 (d), 128.6 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.0 (d), 123.9 (d), 122.5 (s), 116.0 (d), 66.3 (t), 56.1 (d), 44.9 (t), 35.3 (t), 21.1 (q). HRMS calcd $[C_{31}H_{28}N_2O_5S + H]^+$ 541.1791, found 541.1791. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3033 (w), 1752 (vs), 1678 (vs), 1164 (vs). The structure was confirmed by single-crystal X-ray cristallograpy.

3-Carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one ethoxymethyl ester (1g). Obtained from the crude product by precipitation from ethyl ether like a colorless solid (0.35 g, 61 %). Mp 214-216 °C; R_f (1:1, hexane: AcOEt) 0.29. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ 10.48 (s, 1H, NH), 7.50 (d, J = 7.5 Hz, 1H, H5), 7.28 (bd, J = 8.3 Hz, 3H, H7, H12, H16), 7.20 (d, J = 8.3 Hz, 2H, H13, H15), 7.13 (t, J = 7.5 Hz, 1H, H6), 6.80 (d, J = 7.5 Hz, 1H, H8), 5.26 (d, 4.98 J = 6.2 Hz, 1H, H18), 5.21 (d, J = 6.2 Hz, 1H, H18'), 4.93 (dd, J = 10.4, 4.4 Hz, 1H, H3), 3.66 (q, J = 7.0 Hz, 2H, H19), 2.99 (dd, J = 15.0, 10.4 Hz, 1H, H9), 2.33 (s, 3H, Me17), 2.29 (dd, J = 15.0, 4.4 Hz, 1H, H9'), 1.15 (t, J = 7.0 Hz, 3H, Me20); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 169.0 (s), 165.8 (s), 145.3 (s), 134.3 (s), 133.6 (s), 130.6 (d), 129.4 (d), 128.7 (d), 127.5 (d), 123.9 (d), 121.6 (bs), 116.9 (d), 90.0 (t), 66.0 (t), 56.6 (d), 36.3 (t), 21.9 (q), 15.7 (q). MS [EI, *m*/*z* (%)]: 418 (10), 263 (47), 187 (57), 59 (100). HRMS calcd $[C_{20}H_{22}N_2O_6S + Na]^+$ 441.1091, found 441.1098. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3205 (w), 3069 (m), 2980 (m), 1754 (s), 1694 (vs), 1172 (vs).

1-Ethoxymethyl-3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one ethoxymethyl ester (1h). Obtained from the crude product by flash chromatography (hexane: AcOEt, 87:13) like a beige oil (0.24 g, 35 %). R_f (1:1, hexane: AcOEt) 0.54. ^{1}H NMR (399.78 MHz, $CDCl_3$) δ

7.66 (d, *J* = 7.9 Hz, 1H, H5), 7.29 (bs, 1H, H7), 7.28 (bs, 1H, H6), 7.23 (d, *J* = 8.1 Hz, 2H, H12, H16), 7.19 (bd, *J* = 7.4 Hz, 1H, H8), 7.10 (d, *J* = 8.1 Hz, 2H, H13, H15), 5.30 (s, 2H, H18), 5.28 (dd, *J* = 10.3, 4.7 Hz, 1H, H3), 4.95 (d, *J* = 10.7 Hz, 1H, H21), 3.93 (d, *J* = 10.7 Hz, 1H, H21'), 3.73 (q, *J* = 7 Hz, 2H, H19), 3.39-3.26 (m, 2H, H22), 2.62 (dd, *J* = 14.7, 4.7 Hz, 1H, H9), 2.44 (dd, *J* = 14.7, 10.3 Hz, 1H, H9'), 2.33 (s, 3H, Me17), 1.23 (t, *J* = 7.0 Hz, 3H, Me20), 1.07 (t, *J* = 7.0 Hz, 3H, Me23); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 168.0 (s), 166.0 (s), 144.5 (s), 134.3 (s), 133.8 (s), 129.4 (d), 129.2 (d), 128.9 (d), 127.3 (d), 124.8 (d), 124.7 (s), 116.5 (d), 90.1 (t), 72.3 (t), 66.3 (t), 64.4 (t), 56.4 (d), 35.8 (t), 21.6 (q), 15.1 (q). HRMS calcd $[C_{23}H_{28}N_2O_7S + Na]^+$ 499.1509, found 499.1504. FT-IR ($CHCl_3$) $\bar{\nu}$ (cm^{-1}): 3143 (w), 2932 (s), 1742 (s), 1691 (vs), 1169 (s).

1-(3-Methylbut-2-enyl)-3-carboxymethyl-4-tosyl-1,2,3,4-tetrahydroquinoxalin-2-one (3-methylbut-2-enyl) ester (1i). Obtained from the crude product by flash chromatography (85:15, hexane: AcOEt) like a yellow oil (0.35 g, 51 %). R_f (1:1, hexane: AcOEt) 0.8. ^{1}H NMR (399.78 MHz, DMSO-d_6) δ 7.53 (dd, *J* = 7.9, 1.2 Hz, 1H, H5), 7.35 (ddd, *J* = 8.2, 7.5, 1.2 Hz, 1H, H7), 7.28 (d, *J* = 8.3 Hz, 2H, H12, H16), 7.20 (t, *J* = 7.7 Hz, 1H, H6), 7.19 (d, *J* = 8.3 Hz, 2H, H13, H15), 6.68 (d, *J* = 8.2 Hz, 1H, H8), 5.28 (bt, *J* = 7.2, 1H, H19), 5.05 (dd, *J* = 10.2, 4.8 Hz, 1H, H3), 4.52 (dd, *J* = 12.7, 7.2 Hz, 1H, H18), 4.47 (dd, *J* = 12.7, 7.2 Hz, 1H, H18'), 4.08-3.98 (m, 2H, H23, H24), 3.91 (dd, *J* = 15.9, 6.6 Hz, 1H, H23'), 2.59 (dd, *J* = 14.7, 4.8 Hz, 1H, H9), 2.32 (s, 3H, Me17), 2.24 (dd, *J* = 14.7, 10.2 Hz, 1H, H9'), 1.71 (s, 3H, Me22), 1.65 (s, 3H, Me21), 1.60 (s, 3H, Me26), 1.54 (s, 3H, Me27); ^{13}C NMR (100.53 MHz, DMSO-d_6) δ 168.7 (s), 164.5 (s), 145.0 (bs), 139.1 (bs), 135.5 (bs), 134.2 (s), 133.9 (bs), 130.3 (d), 129.2 (d), 129.0 (d), 127.2 (d), 124.1 (d), 123.1 (s), 119.3 (d), 119.0 (d), 116.5 (d), 61.9 (t), 56.6 (d), 39.8 (t), 35.8 (t), 25.9 (q), 25.7 (q), 21.6 (q), 18.3 (q). HRMS calcd for $[C_{27}H_{32}N_2O_5S + H]^+$ 497.2104, found 497.2105. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 2928 (s), 1739 (vs), 1680 (vs), 1385 (vs), 1167 (vs).

(*Z*)-3-(2'-amino-5'-nitrophenylcarbamoyl)propenoic acid (8b). The acid **8b** was prepared in a manner similar to that previously described for **8a**.[12] Obtained from the crude product by precipitation from hexane/acetone like a dark yellow solid (2.12 g, 92 %). Mp 188-189 °C; R_f (4:6:0.1, hexane: AcOEt: formic acid) 0.29. ^{1}H NMR (399.78 MHz, DMSO-d_6) δ 13.21 (bs, 1H, CO_2H), 9.77 (s, 1H, NH), 8.14 (d, *J* = 2.6 Hz, 1H, H6'), 7.89 (dd, *J* = 9.0, 2.6 Hz, 1H, H4'), 6.76 (d, *J* = 9.0 Hz, 1H, H3'), 6.60 (d, *J* = 12.1 Hz, 1H, H3), 6.61-6.56 (bs, 2H, NH_2), 6.26 (d, *J* = 12.1 Hz, 1H, H2); ^{13}C NMR (100.53 MHz, DMSO-d_6) δ 167.2 (s), 165.2 (s), 150.7 (s), 135.9 (s), 134.9 (d), 128.9 (d), 124.2 (d), 123.0 (d), 120.9 (s), 114.2 (d). MS [EI, *m*/*z* (%)]: 251 (14), 233 (54), 153 (100), 80 (48). HRMS calcd for $[C_{10}H_9N_3O_5 + H]^+$ 252.0615, found 252.0812. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3361 (vs), 3250 (vs), 1708 (vs), 1311 (vs), 846 (s).

3-Methylquinoxalin-2-one (10). To solution of **1a** (0.2 g, 0.97 mmol) in ethanol (7 mL), metallic sodium (25 mg, 1.9 mmol) was added. The solution was allowed to mix at rt for 4 h. After 4 h, the product precipitated from the solution like a beige solid (0.12 g, 80 %). Mp 237-238 °C (lit. 221 °C[11], 241-243 °C[3]); R_f (4:6:0.1, hexane: AcOEt: formic acid) 0.50. ^{1}H NMR (399.78 MHz, DMSO-d_6) δ 12.31 (sa, 1H, NH), 7.67 (d, *J* = 8.4 Hz, 1H, H5), 7.45 (td, *J* = 8.4,

1.4 Hz, 1H, H6), 7.27-7.26 (m, 2H, H7, H8), 2.38 (s, 3H, Me); ^{13}C NMR (100.53 MHz, DMSO-d_6) δ 159.8 (s), 155.5 (s), 132.5 (s), 132.2 (s), 129.8 (d), 128.4 (d), 123.6 (d), 115.8 (d), 21.1 (q). MS [EI, *m*/*z* (%)]: 160 (100), 132 (86), 131 (76), 104 (6). HRMS calcd for $[C_9H_8N_2O + H]^+$ 161.0709, found 161.0712. FT-IR (KBr) $\bar{\nu}$ (cm^{-1}): 3310 (b), 2847 (s), 1674 (vs), 1380 (m).

Acknowledgements

This research was partially supported by CONACYT-México (52264).

References

1. Sarges, R.; Lyga, J. W. *J. Heterocycl. Chem*. **1988**, *25*, 1475.
2. (a) TenBrink, R. E.; Im, W. B.; Sethy, V. H.; Tang, A. H.; Carter, D. B. *J. Med. Chem*. **1994**, *37*, 758. (b) Jacobsen, E. J.; TenBrink, R. E.; Stelzer, L. S.; Belonga, K. L.; Carter, D. B.; Im, H. K.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D. *J. Med. Chem*. **1996**, *39*, 158. (c) Jacobsen, E. J.; Stelzer, L. S.; TenBrink, R. E.; Belonga, K. L.; Carter, D. B.; Im, H. K.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D.; Zhong, W. Z.; Mickelson, J. W. *J. Med. Chem*. **1999**, *42*, 1123.
3. Lawrence, D. S.; Copper, J. E.; Smith, C. D. *J. Med. Chem*. **2001**, *44*, 594.
4. (a) Sanna, P.; Carta, A.; Loriga, M.; Zanetti, S.; Sechi, L. *IL Farmaco* **1999**, *54*, 161. (b) *Ibid*. 169. (c) Ali, M. M.; Ismail, M. M. F.; El-Gaby, M. S. A.; Zahran, M. A.; Ammar, Y. A. *Molecules* **2000**, *5*, 864.
5. Carta, A.; Sanna, P.; Gherardini, L.; Usai, D.; Zanetti, S. *IL Farmaco* **2001**, *56*, 933.
6. Patel, M.; McHugh Jr., R. J.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1729.
7. Carta, A.; Sanna, P.; Loriga, M.; Setzu, M. G.; Colla, P. L.; Loddo, R. *IL Farmaco* **2002**, *57*, 19.
8. (a) Olagbemiro, T. O.; Nyakutse, C. A.; Lajide, L.; Agho, M. O.; Chukwu, C. E. *Bull. Soc. Chim. Belg.* **1987**, *96*, 473. (b) Mickelson, J. W.; Jacobsen, E. J.; Carter, D. B.; Im, H. K.; Im, W. B.; Schreur, P. J. K. D.; Sethy, V. H.; Tang, A. H.; McGee, J. E.; Petke, J. D. *J. Med. Chem*. **1996**, *39*, 4654. (c) Lai, J. T. *Synthesis* **1982**, 71.
9. (a) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem*. **1997**, *62*, 3874. (b) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem*. **1998**, *63*, 1172. (c) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **1999**, *64,* 2555.
10. (a) Petasis, N. A.; Patel, Z. D. *Tetrahedron Lett*. **2000**, *41*, 9607. (b) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **2002**, *58*, 221. (c) Tung, C.-L.; Sun, C.-M. *Tetrahedron Lett*. **2004**, *45*, 1159.
11. Nikolaenko, I. V.; Munro, O. Q. *Acta Cryst*. *E.* **2004**, *60*, o92.

12. Santos-Sánchez, N. F.; Salas-Coronado R.; Peña-Hueso, A.; Flores-Parra A. *Acta Cryst. E*. **2007**, *63*, o4156.
13. Krchňák, V.; Szabo, L.; Vágner J. *Tetrahedron Lett*. **2000**, *41*, 2835.
14. Diez-Barra, E.; de la Hoz, A.; Sánchez-Migallón, A.; Tejeda, J. *Synth. Commun.* **1990**, *20*, 2849.
15. Zotov, A. Yu.; Palyulin, V. A.; Zefirov, N. S. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 766.
16. Sheldrick, G. M. SHELX-97, 2nd ed.; Institut für Anorganische Chemie der Universität Tammannstrasse 4, D-3400 Göttingen, Germany, **1998**.

 ©ARKAT USA, Inc.