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Substitutions of fluorine atoms and phenoxy groups in the synthesis of quinoxaline 1,4-di-*N*-oxide derivatives

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Abstract: The unexpected substitution of fluorine atoms and phenoxy groups linked to quinoxaline or benzofuroxan rings is described. The synthesis of 2-benzyl and 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives was based on the classical Beirut reaction. The experimental conditions (reaction solvent and catalyst) were explored with the aim of obtaining the target compounds.

Introduction

Quinoxaline and quinoxaline-1,4-di-*N*-oxide are heterocycles that are usually used in the synthesis of biologically active compounds.[1-4] The quinoxaline moiety is described as a bioisoster of quinoline, naphthyl, benzothienyl and other aromatic rings,[5] and the widespread activity of quinoxaline-1,4-di-*N*-oxide derivatives can be associated with the generation of free radicals.[6]

In our continuing efforts to find quinoxaline-1,4-di-*N*-oxide derivatives with antimycobacterial[7-9] and antiprotozoal activity,[10-14] a series of 2-benzyl-3-methylquinoxaline 1,4-di-*N*-oxide derivatives was proposed. With regard to work carried out by our research team, this series involves the analogues of 2-benzoyl-3-methylquinoxaline 1,4-di-*N*-oxide derivatives in which the carbonyl group has been reduced.[7] In addition, with regard to Carta's paper,[15] this series, together with a series of 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives, could complete the bioisosterism replacements based on Grimm's Hydride Displacement Law (chart 1). This law states that the addition of a hydrogen atom with a pair of electrons (i.e. hydride) to an atom belonging to groups 4A, 5A, 6A, 7A on the Periodic Table, produces an isoelectronic pseudoatom, showing the same physical properties as those present in the column immediately behind the initial atom on the Periodic Table of the Elements.[5]

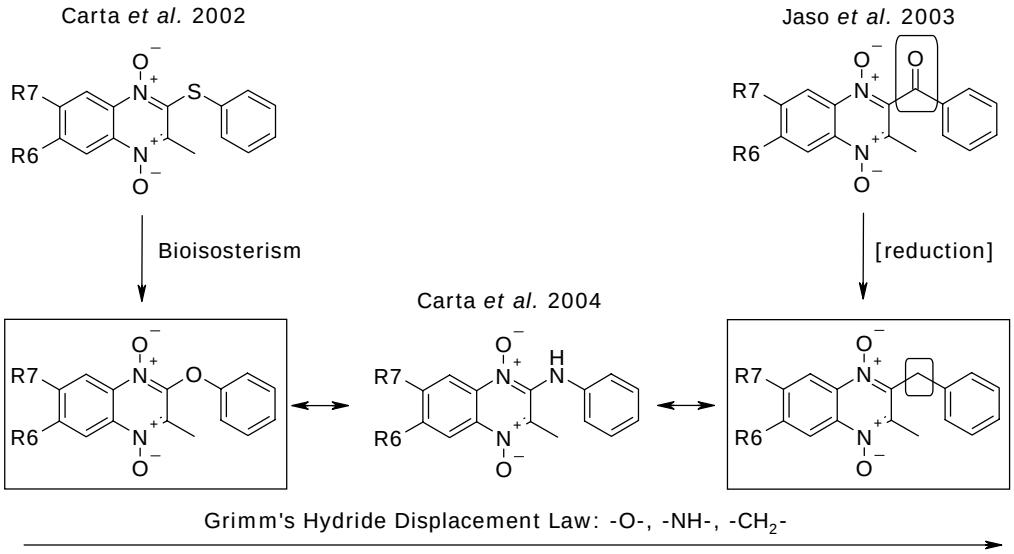

Chart 1. Design of new quinoxaline-1,4-di-*N*-oxide derivatives with antimycobacterial activity.

Results and Discussion

In a continuing effort to synthesize new antitubercular and antiprotozoal drug candidates, the synthesis of 2-benzyl and 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives was proposed. Therefore, equimolar amounts of the appropriate benzofuroxane and bencylacetone (or phenoxy-2-propanone) were added to methanol. The mixture was bubbled in with ammonia gas (chart 2) and then stirred at room temperature. After evaporating to dryness, a crude solid was obtained. It was then washed and purified.

After workup, all of the obtained compounds were chemically characterized by thin layer chromatography (TLC), infrared (IR) and nuclear magnetic resonance (^{1}H-NMR) spectra as well as by elemental microanalysis. From these analyses, it was observed that the reaction with phenoxy-2-propanone failed to give the functionalized 2-phenoxy derivatives; surprisingly, this reaction gave other quinoxaline 1,4-di-*N*-oxide derivatives, with an amino group, instead of the phenoxy moiety, linked to C2 of quinoxaline ring (analyses data in experimental section). It is well know that the phenoxy scaffold is a good leaving group and that the ammonia gas is a potent alkali; the curious part is that first the quinoxaline is formed and later, the substitution occurs (the events could not have occurred in any other way due to the products obtained) (chart 3).

In an attempt to obtain the 2-phenoxy derivatives, the catalyst and the solvent were changed by piperidine and dichloromethane, respectively. In this case, the 2-phenoxy-3-methyl-quinoxaline 1,4-di-*N*-oxide was obtained (chart 2).

The formation of isomeric quinoxaline 1,4-di-*N*-oxide was observed in the case of monosubstituted benzofuroxanes. According to previous reports,[16] we have observed that 7-substituted quinoxaline 1,4-di-*N*-oxide derivatives were prevailing over the 6-isomer, or in the case of the methoxy substituent, only the 7-isomer was formed (NOESY data not shown). In practice, the workup and purification permitted isolation of the 7 isomer.[17]

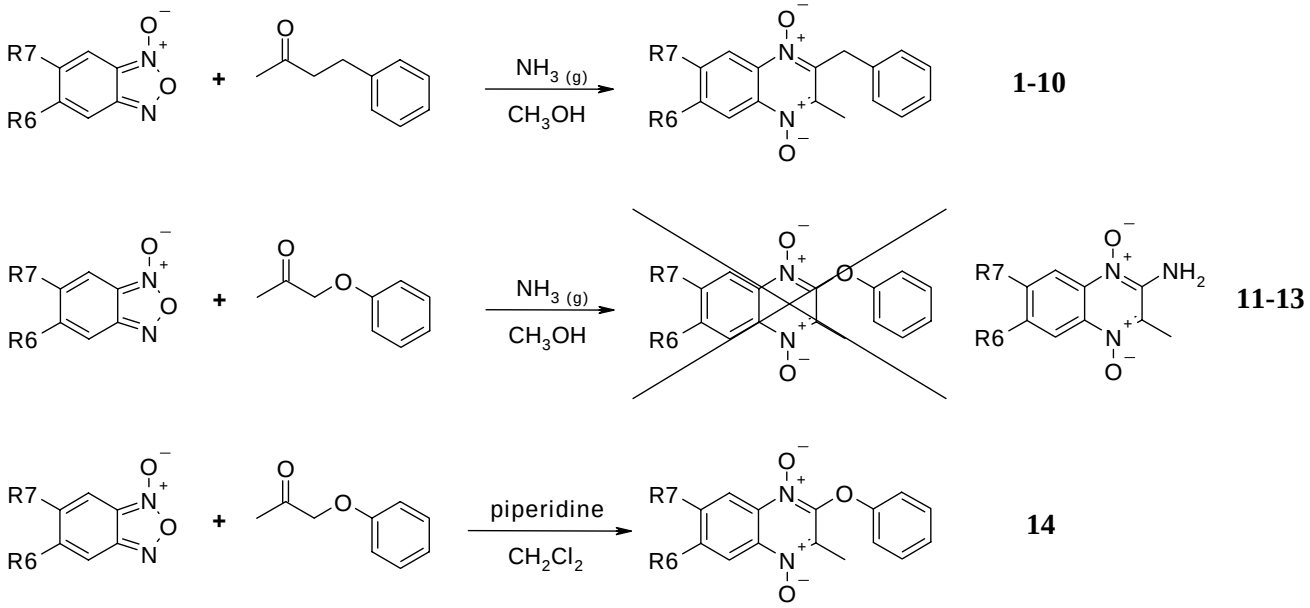

Chart 2. Synthesis of 2-benzyl and 2-phenoxy-3-methylquinoxaline 1,4-di-*N*-oxide derivatives.

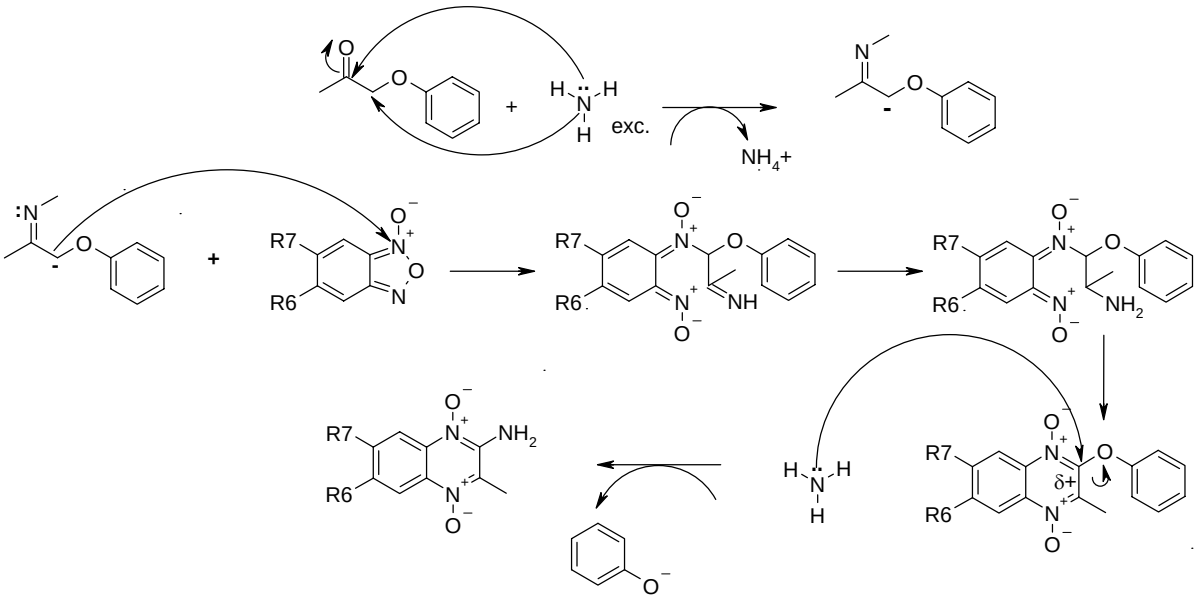

Chart 3. Possible mechanism of reaction for 2-amino-3-methylquinoxaline 1,4-di-*N*-oxide derivatives.

On the other hand, it was also observed that the reaction of difluorobenzofuroxane with benzylacetone in methanol failed to give 2-benzyl-6,7-difluoro-3-methylquinoxaline 1,4-di-*N*-oxide; the ^{1}H-NMR spectra of the obtained compound showed the presence of a methoxy group in the structure and it corresponded with a 6,7-disubstituted quinoxaline; so we thought that, under these conditions, the fluorine atom in position 6 was substituted by a methoxy group from the solvent. The displacement of the fluor atom in position 6 has been observed on other occasions.[18] In an attempt to obtain the 6,7-difluoro derivative, the solvent was changed but keeping the rest of the reaction conditions. In this case, using dichloromethane as reaction solvent, the 2-benzyl-6,7-difluoro-3-methyl-quinoxaline 1,4-di-*N*-oxide was obtained (chart 4).

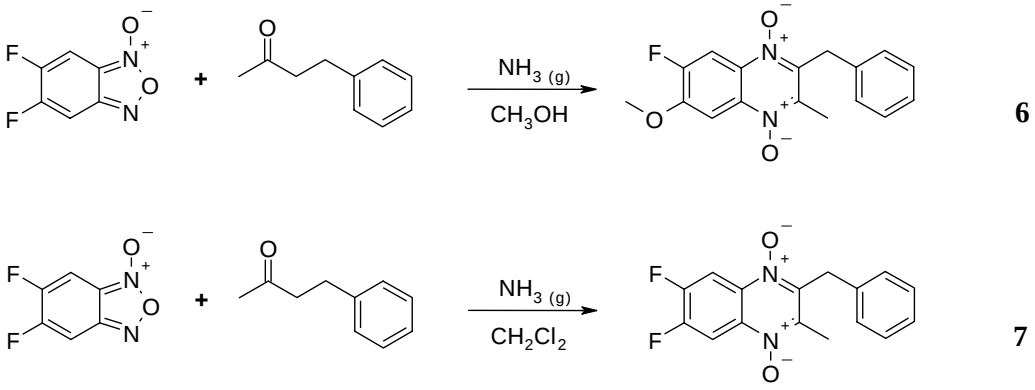

Chart 4. Synthesis of 7-fluoro-6-methoxy and 6,7-difluoro 2-benzyl-3-methylquinoxaline 1,4-dioxides.

Finally, we observed another curiosity using fluorinated compounds. When we attempted to prepare R7(R6)-fluorobenzofuroxane by oxidation of the corresponding fluoronitroaniline as previously described,[19] the obtain compound was R7(R6)-methoxybenzofuroxane. Once again, the methanol was present in the reaction as solvent. So, R7(R6)-fluorobenzofuroxane was prepared by thermal decomposition as reported.[18-20]

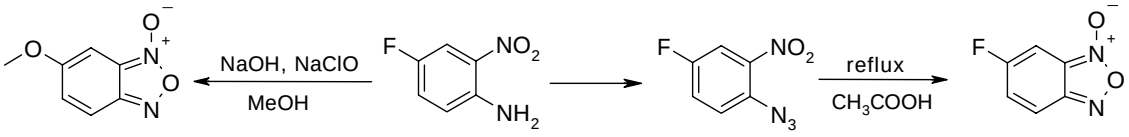

Chart 5. Synthesis of 5(6)-fluorobenzofuroxan from the corresponding o-nitroaniline.

Conclusions

Summarizing, this work clearly demonstrates the tendency of fluorine atoms linked to quinoxaline or benzofuroxane rings to leave their positions and be replaced by a methoxy group when dissolving in an ammonia saturated solution of methanol. In addition, the 2-phenoxyquinoxaline 1,4-di-*N*-oxide derivatives, in the presence of ammonia gas, become 2-aminoquinoxaline 1,4-di-*N*-oxide derivatives.

Experimental Section

All of the synthesized compounds were chemically characterized by thin layer chromatography (TLC), infrared (IR), nuclear magnetic resonance (^{1}H-NMR), mass spectra (MS) and elemental microanalysis (CHN). Alugram SIL G/UV254 (Layer: 0.2 mm) (Macherey-Nagel GmbH & Co. KG. Postfach 101352. D-52313 Düren, Germany) was used for Thin Layer Chromatography and Silica gel 60 (0.040-0.063 mm) for Column flash Chromatography (Merck). The ^{1}H NMR spectra were recorded on a Bruker 400 Ultrashield instrument (400 MHz), using TMS as the internal standard and with DMSO-d^6 and $CDCl_3$ as the solvents; the chemical shifts are reported in ppm (δ) and coupling constants (*J*) values are given in Hertz (Hz). Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), q (quadruplet), dd (double doublet) and m (multiplet). The IR spectra were

performed on a Thermo Nicolet Nexus FTIR (Madison, USA) in KBr pellets; the frequencies are expressed in cm^{-1}. The mass spectra were measured on an Agilent Technologies Model MSD/DS 5973N (mod. G2577A) mass spectrometer with direct insertion probe (DIP) (Waldbronn, Germany) and the ionization method was electron impact (EI, 70 eV). Elemental microanalyses were obtained on an Elemental Analyzer (Leco CHN-900, Tres Cantos, Madrid, Spain) from vacuum-dried samples. The analytical results for C, H, and N, were within ± 0.4 of the theoretical values. Chemicals were purchased from Panreac Química S.A. (Montcada i Reixac, Barcelona, Spain), Sigma-Aldrich Química, S.A., (Alcobendas, Madrid), Acros Organics (Janssen Pharmaceuticalaan 3a, 2440 Geel, België) and Lancaster (Bischheim-Strasbourg, France).

General synthesis of 2-benzyl-3-methylquinoxaline 1,4-di-N-oxide derivatives (1-10).[11,15]

Equimolar amounts (3.0–117.0 mmol) of the appropriate benzofuroxan and bencylacetone were added to 20 mL of methanol (or 20 mL of dichloromethane for 6,7-difluoro derivative). The mixture were bubbled in with ammonia gas for 10 minutes and then stirred at room temperature for 4 hours. After evaporating to dryness under reduced pressure, a crude solid was obtained. It was then washed by adding diethyl ether and purified by recrystallization from a mixture of methanol/dichloromethane.

General synthesis of 2-amino-3-methylquinoxaline 1,4-di-N-oxide derivatives (10-13).

Equimolar amounts (3.0–117.0 mmol) of the appropriate benzofuroxan and phenoxy-2-propanone were added to 20 mL of methanol. The mixture were bubbled in with ammonia gas for 10 minutes and then stirred at room temperature for 4 hours. After evaporating to dryness under reduced pressure, a crude solid was obtained. It was then washed by adding diethyl ether and purified by recrystallization from a mixture of methanol/dichloromethane.

General synthesis of 2-phenoxy-3-methylquinoxaline 1,4-di-N-oxide derivatives (14).

Equimolar amount of phenoxy-2-propanone was added to a solution of the appropriate benzofuroxan (3.0–117.0 mmol) in dry dichloromethane (35 mL). The mixture was allowed to stand at 0 ºC. Piperidine was added dropwise (1 mL), and the reaction mixture was stirred at room temperature in darkness for 4 hours. After evaporating to dryness under reduced pressure, a crude solid was obtained. It was then washed by adding diethyl ether (or n-hexane), affording the target compound. The obtained precipitate was purified by recrystallization from a mixture of methanol/dichloromethane.

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