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First synthesis of 2-phosphonylated quinoxaline 1,4-dioxides: an extension to the Beirut reaction

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ABSTRACT

An extension of the Beirut reaction for the preparation of the first members of the 2-phosphonylated quinoxaline 1,4-dioxide series is described. Contrary to their carboxylated equivalents, preparation of these new compounds could not be achieved under basic conditions but required the use of powdered molecular sieves. Good and reproducible yields were obtained only when the initial suspension in THF was transformed into a pasty film by slow evaporation of ca. 90% of the initial solvent volume.

1. Introduction

Among heteroaryls, quinoxaline 1,4-dioxides corresponding to general scaffold **1** are endowed with many biological properties that in particular largely encompass by their diversity the properties of the non-oxgenated quinoxalines.[1] Indeed, already recognized in the 1940's for their antibacterial activities,[2] many quinoxaline dioxide derivatives have gained much attention for their antimycobacterial, anticandida, antiprotozoal (especially antimalaria) as well as anticancer properties.[1,3] Most bioactive members of this family possess either an oxo or a sulfonyl group in position 2 as in the anticandida phenylsulfone **2**,[3a] the antitubercular benzylcarboxylate, and benzylcarboxamide **3**[3b,c] or the recently described tumor-specific propenoyl derivative **4**[3d] (Fig. 1).

Considering the importance of phosphonate derivatives in medicinal chemistry as bioisosters of carboxylates and sulfones,[4] it is surprising that no 2-phosphonylated quinoxaline 1,4-dioxides have been reported so far. To our knowledge, as indicated in Figure 2, only a handful of phosphonates derived from quinoxalines have been described so far.[5]

We disclose herein our efforts to synthesize 2-phosphonylated quinoxaline 1,4-dioxides.

2. Results and discussion

In order to prepare 2-phosphonylated quinoxaline 1,4-dioxides, we first tested the nucleophilic substitutions of chlorine by sodium dimethyl phosphonate, freshly prepared from dimethylphosphite by the action of NaH in THF, in four chloroquinoxalines **5**–**8**. For that purpose, chloroquinoxalines **6**–**8** were prepared simultaneously in excellent overall yield by oxidizing commercial chloroquinoxaline **5** using Caro's acid in concentrated sulfuric acid (Scheme 1).[6] Under these conditions, we were pleased to isolate the recently described dioxide derivative **8**,[7] albeit in low yield, besides the expected pair of chloro monoxides **6** and **7**.

This series of experiments is summarized in Scheme 2. After exposure to an excess of sodium dimethyl phosphonate at room temperature, quinoxalines **5**, **7**, and **8** did not yield significant amounts of phosphonate derivatives. The parent quinoxaline **5** was recovered entirely whereas oxides **7** and **8** were simply converted into **5** and **6**, respectively, following a deoxygenation reaction similar to the action of trimethylphosphite or phosphorus trichloride on quinoxaline oxide derivatives, as already reported.[8] The experiment with chloroquinoxaline monoxide **6** was more gratifying, yielding dimethyl(quinoxalin-2-yl)phosphonate **10** in good yield along with trace amounts of monoxide **9**. Using a lower temperature and/or only one equivalent of $NaP(O)(OMe)_2$ the reaction was very sluggish, giving in particular no better yield in phosphonate **9**.[9] Utilization of lithium dimethyl phosphonate, prepared by deprotonation (LiHMDS) of dimethylphosphite,[10] or dimethylphosphite in the presence of K_2CO_3, Et_3N, or CsF in place of sodium dimethyl phosphonate also proved disappointing, giving at best a low yield of **10**.

We then examined the effect of replacing Cl^- by other nucleofuges: after having checked that 2-fluoroquinoxaline monoxide was far too unstable for being used,[11] we performed a few experiments starting from 2-iodoquinoxaline monoxide, obtained in 85%

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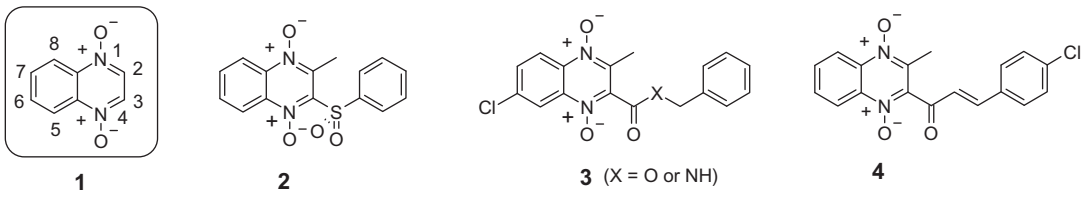


Figure 1. The quinoxaline 1,4-dioxide scaffold **1** and examples of biologically relevant 2-substituted quinoxaline 1,4-dioxides.

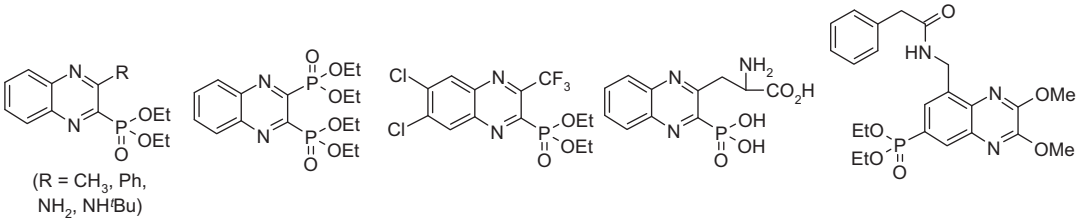
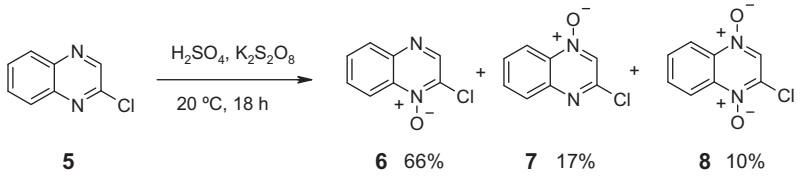
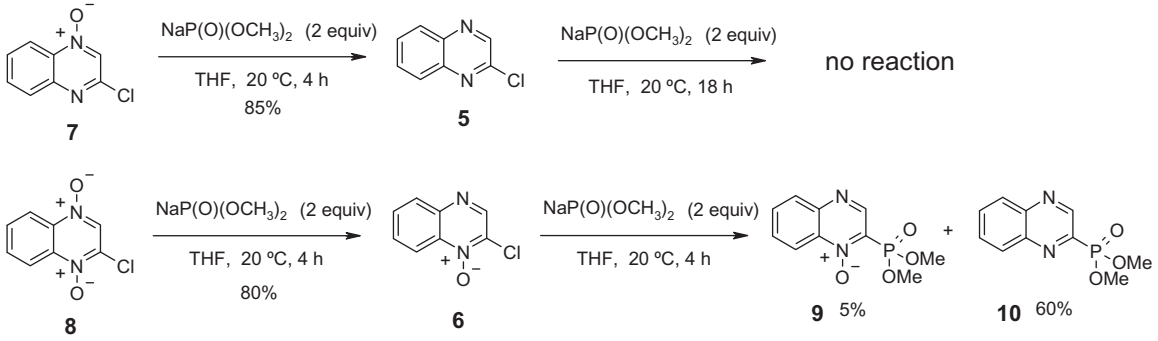


Figure 2. Quinoxaline-derived phosphonates described in the litterature.[5]



Scheme 1. Synthesis of chloroquinoxaline oxides.



Scheme 2. Action of sodium dimethyl phosphonate on chloroquinoxalines.

yield from **6** by the action of sodium iodide in the presence of HI.[12] Action of $NaP(O)(OMe)_2$ resulted mainly in deiodination, leading to quinoxaline monoxide, whereas pallado-catalyzed Hirao cross-coupling trials were disappointing, offering at best a sluggish conversion into phosphonates **9** and **10**.[13]

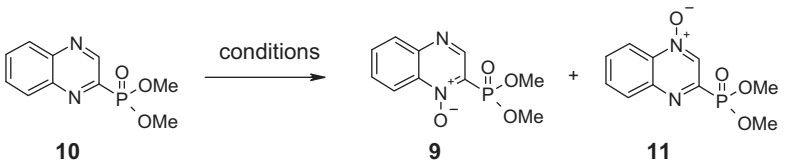
We then investigated oxidizing reactions on phosphonate **10**. As presented in Table 1, by using conditions previously selected for the preparation of the chloroquinoxalines **6**–**8**, we could prepare **9** in 30% yield, while recovering the starting phosphonate also in 30% yield (entry 3). Forcing the experimental conditions, as well as using only a slight excess of potassium persulfate proved unsatisfactory (entries 4 and 6) and adding methanol in the medium, in the hope of esterifying any phosphonic acid derivatives that could have been formed, yielded only a complex mixture (entry 7). Using *m*CPBA (entry 1) or better freshly prepared peracetic acid (entry 2) enabled us to prepare the isomeric monoxide **11** in very good yield.

Although this first set of experiments enabled us to prepare, for the first time, two phosphonates attached to a quinoxaline monoxide moiety,unfortunately no dioxide derivatives were obtained. We decided to investigate at this stage a modification of the Beirut reaction. This reaction which involves the condensation of a β-ketoester on benzofuroxan under basic conditions has already been frequently used in the synthesis of quinoxaline dioxide derivatives.[14]

Utilization of $Ca(OH)_2$ or NaOEt as a base, as often recommended for the Beirut reaction, unfortunately led to an unexploitable complex mixture starting with dimethyl 2-oxopropylphosphonate. By using either cesium carbonate or cesium fluoride as a base, we could obtain the 2-methylquinoxaline dioxide **12** in good yield probably via a transient phosphonylated alcoholate, as indicated in Scheme 3. No traces of phosphonylated quinoxalines were detected under these conditions.

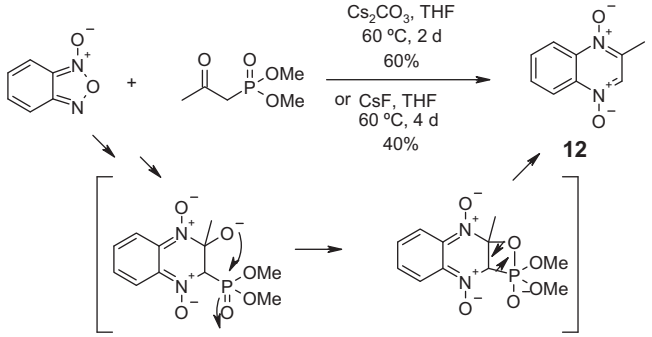
In the hope of trapping by protonation the transient alkoxide, thus avoiding phosphonate elimination, we replaced the basic salt and instead we used molecular sieves 3 Å.[15] We were pleased to isolate under these conditions the desired phosphonate **13a** as a yellow solid, along with trace amounts of **12** and the dimethyl-

Table 1
Oxidation experiments on dimethyl(quinoxalin-2-yl)phosphonate



Entry	Conditions	**10**[a] (%)	**9**[b] (%)	**11**[b] (%)
1	*m*CPBA/$CHCl_3$/40 °C/3 d	30	nd[c]	30
2	**AcOH/Ac_2O/H_2O_2 (35%) 50 °C/20 h**	12	2	**86**
3	**H_2SO_4/$K_2S_2O_8$ (3 equiv) 20 °C/16 h**	30	**30**	nd
4	H_2SO_4/$K_2S_2O_8$ (5 equiv) 20 °C/16 h	nd	10	nd
5	H_2SO_4/$K_2S_2O_8$ (3 equiv) 4 °C/3 d	60	15	nd
6	H_2SO_4/$K_2S_2O_8$ (1.5 equiv) 20 °C/48 h	44	6	nd
7	MeOH/H_2SO_4/$K_2S_2O_8$ (5 equiv)/20 °C/16 h	nd	nd	nd

[a] Recovered starting material.
[b] Yield of isolated product.
[c] Not detected.



Scheme 3. First tentatives of Beirut reaction with dimethyl 2-oxopropylphosphonate.

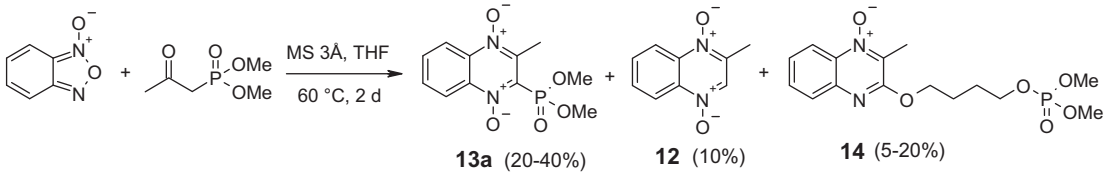
phosphate **14** resulting from the incorporation by an as yet unknown mechanism of one molecule of THF (Scheme 4).

On repeating this experiment, we encountered difficulties to get reproducible yields (see Scheme 4). We examined several reaction conditions including varying the temperature, the nature of the molecular sieves (3–5 Å, in powder or in beads, used as such or preactivated) as well as using acetonitrile as a solvent. None of these conditions improved the reproducibility of the reaction and the yield of **13a**. The reaction mixture being heterogenous, we suspected that stirring could be responsible at least for the poor reproducibility of these experiments. We then performed trials without stirring, confining the reacting medium to a pasty film after evaporation of ca. 90% of the initial solvent volume containing the benzofuroxan, dimethyl 2-oxopropylphosphonate, and molecular sieves in powder. As shown in Table 2, these changes proved very fruitful. We first investigated experiments in a film of THF at 50 °C during one day, checking before all the decisive role of the molecular sieves (entry 1). In the presence of molecular sieves, a very good yield of phosphonate **13a** was observed with the formation of a small amount of the dephosphorylated compound **12**. Interestingly, no traces of **14** were detected (entry 2). Completing the evaporation of the solvent to dryness resulted in a poorer yield in phosphonate (entry 3). The best result was obtained in THF after three days at 30 °C (entry 4), minimizing in particular the formation of the side product **12**. We then tested a few solvents (entries 5–10) but could not reach the efficiency of experiments in THF. In methanol, the reaction was particularly fast but gave **12** as a major product which probably arose from the decomposition of phosphonate **13a** by nucleophilic attack of MeOH on the phosphonate moiety.[16]

We then investigated the reactivity of a few β-ketophosphonates under the optimized previous conditions (Table 3).

In most cases, the reaction proceeded very well, giving good yields of quinoxaline dioxide derivatives.[9,17] In the case of R = H, a complex mixture was obtained after one day with no formation of quinoxaline derivatives whereas for R = OCH_3, the starting products were entirely recovered. In the case of R = Ph, it was better to stop the reaction after 4 h, thus enabling the recovery of half of the starting phosphonate: a longer reaction time did not afford a better yield in the quinoxaline derivative **13g** but resulted in lower yields of recovery of the starting phosphonate.[18]

In summary, we have prepared the first quinoxaline dioxide-derived phosphonates. This offers stimulating perspectives in medicinal chemistry, taking into account the variety of biological properties attributed to quinoxaline dioxide derivatives. Although our attempts to prepare them by oxidation of quinoxaline or quinoxaline monoxide precursors failed, we developed with success an extension of the Beirut reaction by using molecular sieves instead of the much more classically used basic conditions. In order to reach reproducible and good yields in phosphonylated quinoxaline dioxides, the reacting medium had to be confined to a pasty film obtained by slow evaporation of 90% of the initial suspension into THF. We are currently exploring the chemistry of these new derivatives.



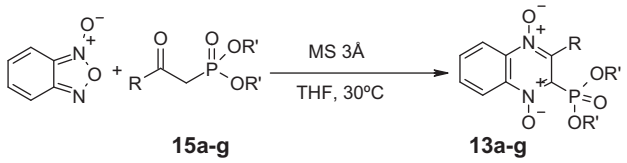
Scheme 4. First successful Beirut reaction with dimethyl 2-oxopropylphosphonate.

Table 2
Optimization studies for the synthesis of phosphonate **13a**

Entry	Solvent	*T* (°C)/time (days)	Conversion[b] (%)	Yield[b] (%) **13a**/**12**
1[c]	THF	50/1	0	0/0
2	THF	50/1	83	77/6
3[d]	THF	50/1	68	58/10
4	**THF**	**30/3**	**83**	**79/4**
5	CH_3CN	30/2	45	36/9
6	CH_3CN/H_2O (95:5, v/v)	40/1	37	6/31
7	CH_3OH	30/2	84.5	2.5/82
9	Toluene	50/1	82	68/14
10	1,4-Dioxane	50/1	47	38/9

[a] Conditions: benzofuroxan (0.65 mmol), phosphonate (0.3 mmol), preactivated molecular sieves (0.3 g); solvent (2 mL) is added and concentrated to ca. 0.2 mL.
[b] Based on NMR analysis of the crude mixture.
[c] No molecular sieves were added.
[d] The medium was evaporated to dryness.

Table 3
Syntheses of 3-substituted-1,4-dioxoquinoxaline-2-dialkylphosphonates[a]



β-Ketoester	R	R′	Time (day)	Yield[b] (%)
15a	CH_3	CH_3	3	79 (70)
15b	CH_3	C_2H_5	3	85 (75)
15c	C_2H_5	C_2H_5	3	73 (63)
15d	C_5H_{11}	CH_3	5	68 (43)
15e	H	C_2H_5	1	0[c]
15f	OCH_3	CH_3	1	0[d]
15g	Ph	CH_3	0.25	45 (42)[e]

[a] Conditions: see Table 2.
[b] Yield based on NMR analysis of the crude mixture (isolated yield after chromatography).
[c] No traces of **13e** and only 5% of **15e**.
[d] Compound **15f** was completely recovered.
[e] Half of the starting phosphonate **15g** was recovered; longer reaction times resulted in no improvement in the yield in **13g**.

Acknowledgments

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9. *Selected analytical data*:
2-(Dimethyl)phosphonyl-quinoxaline **10**:
^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.26 (s, 1H), 8.16 (dd, 1H, J = 2.1 and 7.8 Hz), 8.07 (dd, 1H, J = 2.1 and 7.8 Hz), 7.8 (m, 2H), 3.93 (d, 6H, J = 11.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.5 (d, J = 222.7 Hz), 145.9 (d, J = 27.7 Hz), 142.8 (d, J = 2.5 Hz), 142.0 (d, J = 21.3 Hz), 132.0, 130.7, 129.9, 129.3, 53.7 (d, J = 6.1 Hz); ^{31}P NMR ($CDCl_3$, 162.1 MHz) δ 12.0; HRMS calcd for $C_{10}H_{12}N_2O_3P$, 239.0580, found 239.0588.
2-(Dimethyl)phosphonyl-quinoxaline 1-*N*-oxide **9**:
^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.06 (d, 1H, J = 2.4 Hz), 8.58 (dd, 1H, J = 1.2 and 8.6 Hz), 8.17 (dd, 1H, J = 1.2 and 8.6 Hz), 7.91 (td, 1H, J = 1.4 and 6.9 Hz), 7.79 (td, 1H, J = 1.4 and 6.9 Hz), 4.05 (d, 6H, J = 11.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2 (d, J = 11.9 Hz), 146.6, 137.2 (d, J = 2.8 Hz), 133.1, 131.1 (d, J = 210.6 Hz), 130.7, 130.2, 118.9, 54.6 (d, J = 5.6 Hz); ^{31}P NMR ($CDCl_3$, 162.1 MHz) δ 8.6; HRMS calcd for $C_{10}H_{12}N_2O_4P$, 255.0529, found 255.0532.
3-Methyl-2-[(dimethyl)phosphonyl]-quinoxaline 1,4-di-*N*-oxide **13a**:
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.63 (dd, 1H, J = 1.2 and 8.6 Hz), 8.56 (dd, 1H, J = 1.2 and 8.6 Hz), 7.90 (ddd, 1H, J = 1.4, 7.2 and 8.6 Hz), 7.83 (ddd, 1H, J = 1.4, 7.2 and 8.6 Hz), 4.03 (d, 6H, J = 11.7 Hz), 2.99 (d, 3H, J = 1.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.1 (d, J = 19.7 Hz), 138.2 (d, J = 2.0 Hz), 136.8 (d, J = 9.1 Hz), 133.4, 133.3 (d, J = 211.5 Hz), 131.3, 120.5 (d, J = 1.3 Hz), 120.4, 54.8 (d, J = 6.4 Hz), 15.4; ^{31}P NMR ($CDCl_3$, 162.1 MHz) δ 7.9; HRMS calculated for $C_{11}H_{13}N_2O_5P$, 284.0562, found 284.0556.
3-Methyl-2-[(diethyl)phosphonyl]-quinoxaline 1,4-di-*N*-oxide **13b**:
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.63 (dd, 1H, J = 1.2 and 8.6 Hz), 8.55 (dd, 1H, J = 1.2 and 8.6 Hz), 7.89 (ddd, 1H, J = 1.2, 6.9 and 8.6 Hz), 7.81 (ddd, 1H, J = 1.2, 6.9 and 8.6 Hz), 4.42 (m, 4H), 3.02 (d, 3H, J = 1.4 Hz), 1.42 (td, 6H, J = 0.7 and 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.0 (d, J = 20.0 Hz), 138.0 (d, J = 2.0 Hz), 137.0 (d, J = 9.0 Hz), 134.1 (d, J = 209.9 Hz), 133.2, 131.2, 120.5, 120.3, 64.7 (d, J = 6.0 Hz), 16.4 (d, J = 6.0 Hz), 15.4; ^{31}P NMR ($CDCl_3$, 162.1 MHz) δ 4.9; HRMS calcd for $C_{13}H_{17}N_2O_5P$, 312.0875, found 312.0870.
3-Ethyl-2-[(diethyl)phosphonyl)]-quinoxaline 1,4 di-*N*-oxide **13c**:
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.62 (dd, 1H, J = 1.2 and 8.6 Hz), 8.54 (dd, 1H, J = 1.2 and 8.6 Hz), 7.89 (ddd, 1H, J = 1.4, 7.1 and 8.6 Hz), 7.81 (ddd, 1H, J = 1.4, 7.1 and 8.6 Hz), 4.43 (m, 4H), 3.58 (q, 2H, J = 7.2 Hz), 1.42 (t, 6H, J = 7.1 Hz), 1.36 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.5 (d, J = 20.1 Hz), 138.3 (d,

J = 2.0 Hz), 137.1 (d, *J* = 9.0 Hz), 133.9 (d, *J* = 210.9 Hz), 133.2, 131.2, 120.6 (d, *J* = 0.5 Hz), 120.5 (2 carbons), 64.6 (d, *J* = 6.0 Hz), 22.0, 16.4 (d, *J* = 8.0 Hz), 10.9; ^{31}P NMR ($CDCl_3$, 162.1 MHz) δ 5.0; HRMS calcd for $C_{14}H_{19}N_2O_5P$, 326.1032, found 326.1028.

3-Phenyl-2-[(diethyl)phosphonyl)]-quinoxaline 1,4 di-*N*-oxide **13g**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.63 (m, 2H), 7.93 (ddd, 1H, *J* = 1.6, 6.9 and 8.6 Hz), 7.88 (ddd, 1H, *J* = 1.6, 6.9 and 8.6 Hz), 7.53 (m, 5H), 4.22 (m, 2H), 4.99 (m, 2H), 1.10 (td, 6H, *J* = 0.5 and 7.2 Hz); ^{31}P NMR ($CDCl_3$, 162.1 MHz) δ 3.9; HRMS calcd for $C_{18}H_{19}N_2O_5P$, 374.1032, found 374.1024.

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12. Experiments run without adding HI resulted in no conversion into 2-iodoquinoxaline monoxide. This latter compound has already been prepared, albeit in lower yield, by thermal decomposition of the corresponding 2-diazonium fluoroborate (Balz–Schiemann reaction).
13. A very poor conversion (<10%) into phosphonates was observed using $Pd(OAc)_2$/dppf, as recently precognized for the synthesis of heteroarylphosphonates by Hirao cross-coupling: Belabassi, Y.; Alzghari, S.; Montchamp, J.-L. *J. Organomet. Chem.* **2008**, *693*, 3171–3178. Switching dppf to xantphos doubled the yield of the reaction.
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15. Utilization of molecular sieves for the Beirut reaction has been reported by M. Hasegawa's group: (a) Takabatake, T.; Hasegawa, Y.; Hasegawa, M. *J. Heterocycl. Chem.* **1993**, *30*, 1477–1479; (b) Takabatake, T.; Miyazawa, T.; Hasegawa, M. *J. Heterocycl. Chem.* **1996**, *33*, 1057–1061; (c) Hasegawa, M.; Takabatate, T.; Miyazawa, T. *Yakugaku Zasshi* **2001**, *121*, 379–393.
16. Subjecting phosphonate **13a** to treatment in methanol in the presence of molecular sieves under reaction conditions yielded a complete conversion into 2-methyl-quinoxaline 1,4-di-*N*-oxide **12**.
17. We noted a good stability at room temperature of reference phosphonate **13a** in solution into THF, $CHCl_3$, or MeOH.
18. The reaction appeared quite sluggish in the case of R = *i*Pr or cyclopropyl: we observed in NMR on prolonged reaction time a complex mixture containing less than 15% of the desired phosphonate.