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SHORT COMMUNICATION

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Carbene-Catalyzed Aroylation of a 2-Chloroquinoxaline *N*-Oxide with Aromatic Aldehydes at Room Temperature[‡]

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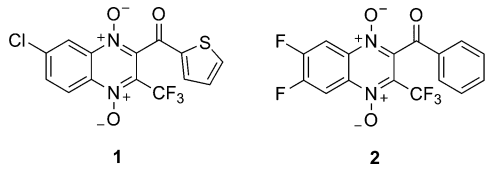
Starting from easily accessible 2-chloro-3-(cyclopentyloxy)-7-fluoroquinoxaline 1-oxide, 12 new biologically promising aroylquinoxaline *N*-oxides were synthesized through carbene-catalyzed aroylation of the chloro nitrone unit with different aromatic aldehydes in the presence of 1,3-dimethylimidazolium iodide as the carbene precursor. The optimized reaction conditions tolerated a broad bandwidth of aldehydes and allowed the synthesis of the corresponding ketones in yields up to 87 %. Studies of their biological activities resulted in interesting specific cytotoxic effects against tumor cell lines.

Introduction

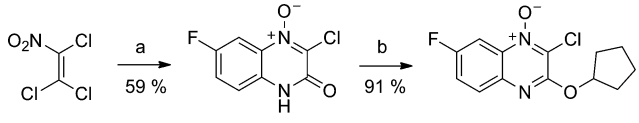
Although quinoxalines are rarely found in nature, such as the antibiotic echinomycin, which was first isolated from *Streptomyces echinatus* in 1957,[1] a large number of quinoxaline derivatives have been synthesized through various synthetic routes.[2] Several examples of this important class of N-heterocycles show highly diverse properties and are able to act, for example, as anticancer agents[3] or as antagonists for certain receptors in the human organism such as histamine H4,[4] AMPA,[5] or Interleukin-8.[6] The easily accessible quinoxaline *N*,*N*′-dioxides out of the Beirut reaction of benzofurazan *N*-oxide with appropriate nucleophiles[7] are also interesting representatives of the quinoxaline class that show, among others, cancerostatic properties such as thienylcarbonyl-substituted quinoxaline 1,4-dioxide **1** (Figure 1).[8] Beyond that, benzoylated *N*,*N*′-dioxide **2** was reported to act as an antitrypanosomatid agent against the pathogen of the Chagas disease *Trypanosoma cruzi*.[9]

During our ongoing studies on the synthesis of biologically active fluorinated quinoxaline *N*-monooxides,[10] our aim was to synthesize structurally similar aroylquinoxalines by means of a C–C coupling reaction of 2-chloro-3-(cyclopentyloxy)-7-fluoroquinoxaline 1-oxide (**5**). This versatile building block is easily accessible on a multigram scale by the previously reported annulation reaction of 1,1,2-trichloro-2-nitroethylene (TCNiE, **3**) with *p*-fluoroaniline[11] and subsequent *O*-alkylation of the obtained quinoxalinone *N*-oxide scaffold with cyclopentanol under Mitsunobu conditions[10] (Scheme 1).



1 **2**

Figure 1. Reported bioactive aroylated quinoxaline *N*,*N*′-dioxides.



3 **4** **5**

Scheme 1. Synthesis of 2-chloro-3-(cyclopentyloxy)-7-fluoroquinoxaline 1-oxide (**5**) starting from TCNiE (**3**). Reagents and conditions: (a) 4-fluoroaniline, NEt_3, (MeOH), 40 °C; (b) cyclopentanol, diethyl azodicarboxylate, PPh_3, (THF), 0–40 °C.

In 1990, Miyashita and co-workers published an efficient method for the nucleophilic aroylation of 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidines with aromatic aldehydes in the presence of 1,3-dimethylbenzimidazolium iodide, which forms a catalytically active carbene species by reaction with an appropriate base.[12] Later, the same research group applied this methodology to the synthesis of 4-aroylcinnolines, 1-aroylphthalazines, and 2-aroylquinoxalines by using aromatic aldehydes as substrates and catalytic amounts of 1,3-dimethylimidazolium iodide.[13] Inspired by these good results, we wanted to investigate the hitherto unknown nucleophilic aroylation of the chloro nitrone unit of our easily accessible chloroquinoxaline 1-oxide **5**.

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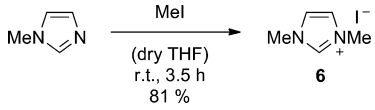
Results and Discussion

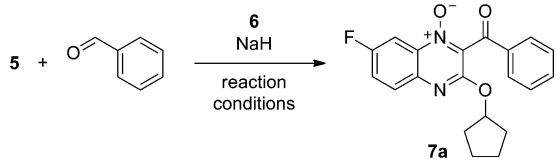
At first, we started to synthesize the required carbene precursor 1,3-dimethylimidazolium iodide (**6**) by reaction of 1-methylimidazole with methyl iodide in THF. The almost quantitatively obtained and very hygroscopic crude product had to be recrystallized owing to trace amounts of water that could not be completely removed by washing the salt with different solvents such as dry *n*-hexane and dry Et_2O. Dry isopropyl alcohol proved to be the best solvent for the recrystallization process under nitrogen, which led to the desired imidazolium salt **6** in 81% yield and in excellent purity according to analysis by NMR spectroscopy (Scheme 2).



Scheme 2. Alkylation of 1-imidazole with methyl iodide.

Next, we applied the reported conditions for the aroylation of 2-chloroquinoxaline[13] to chloroquinoxaline *N*-oxide **5** by using the synthesized azolium salt in catalytic amounts. Although the reaction of **5** with benzaldehyde in the presence of sodium hydride and catalyst **6** in dry THF took place under reflux conditions, the desired benzoylated product **7a** could only be obtained in a moderate yield after a reaction time of 2 h besides large amounts of unreacted starting material (Table 1, Entry 1). Unfortunately, prolongation of the reaction time did not significantly affect the outcome of this reaction. In contrast, the change to DMF as a more polar aprotic solvent significantly increased the reaction yield from 20 to 74% within a comparable reaction time and temperature. Surprisingly, a decrease in the reaction temperature to room temperature allowed the full conversion of **5** within 30 min and gave **7a** in a very good yield of 86% (Table 1, Entry 4).

Table 1. Optimization of the carbene-catalyzed aroylation of *O*-alkylated chloroquinoxaline *N*-oxide **5** with benzaldehyde.[a]

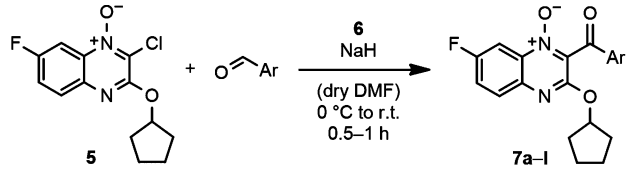


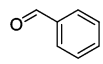
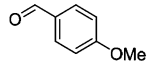
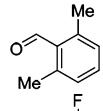
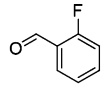
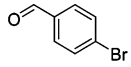
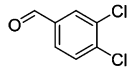
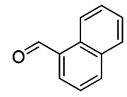
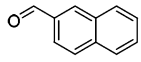
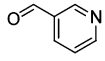
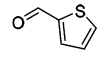
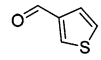
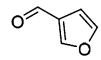
Entry	Solvent	Temperature	Time [h]	Yield [%][b]
1	dry THF	reflux	2	20
2	dry THF	reflux	8	23
3	dry DMF	65 °C	3	74
4	dry DMF	r.t.	0.5	86

[a] Reaction conditions: PhCHO (1.2 equiv.), NaH (1.3 equiv.), 1,3-dimethylimidazolium iodide (**6**; 0.3 equiv.). [b] Yield of isolated product after column chromatography.

These optimized reaction conditions were successfully applied to a number of different aromatic and heteroaromatic aldehydes, which allowed the isolation of aroylated quinoxaline *N*-oxides **7a**–**l** in moderate to very good yields (Table 2). In general, the unsubstituted benzaldehyde, electron-rich, and monohalogenated substrates such as 4-bromo- and 2-fluorobenzaldehyde gave the best results within short reaction times (0.5–1 h). Whereas bicyclic 2-naphthaldehyde gave the corresponding ketone **7h** in 87% yield, isomeric 1-naphthaldehyde led to the desired product **7g** in a lower yield of 60% under identical conditions, most likely because of the higher steric hindrance of the α-naphthoyl group relative to that of the β-naphthoyl substituent (Table 2, Entries 7 and 8).

Table 2. Carbene-catalyzed aroylation reaction of *O*-alkylated quinoxaline *N*-oxide **5** with different aldehydes.



Entry	ArCHO	Product	Yield [%][a]
1		**7a**	86
2		**7b**	75
3		**7c**	87
4		**7d**	78
5		**7e**	84
6		**7f**	54
7		**7g**	60
8		**7h**	87
9		**7i**	48
10		**7j**	77
11		**7k**	68
12		**7l**	61

[a] Yield of isolated product after column chromatography.

As expected, nitro-substituted arenecarbaldehydes such as 4-nitrobenzaldehyde were not tolerated as substrates in this base-induced aroylation reaction because of the nitro group's reactivity towards sodium hydride as a strong base. Surprisingly, also the reduced analogue, 4-(dimethylamino)-benzaldehyde, could not be converted into the correspond-

ing ketone. We were pleased that a few heterocyclic substrates such as nicotinaldehyde, thiophenecarbaldehydes, and 3-furancarbaldehyde could also be applied to the nucleophilic aroylation of **5**.

The newly synthesized aroylquinoxaline *N*-oxides were evaluated for their biological activity with several microorganisms (*Bacillus subtilis* DSM10, *Pseudomonas aeruginosa* DSM50071, *Escherichia coli* TolC HZI strain, *Staphylococcus aureus* DSM346, *Chromobacterium violaceum* DSM30191, *Candida albicans* DSM1386, and *Mucor hiemalis* DSM2656), four mammalian cell lines, one established mouse cell line, two human tumor cell lines, and primary healthy endothelial cells. Although the compounds were not active against the microorganisms, many of the aroylquinoxaline *N*-oxides had clear cytotoxic effects (Table 3). The only compound that showed no toxicity was pyridyl derivative **7i**. Interestingly, some compounds displayed a striking preference for tumor cell lines over normal human cells (HUVEC) and the mouse fibroblast cell line L-929; for example, **7a** and **7b** showed good activity with KB-3-1, which is a human cervix carcinoma cell line, and A-549, human lung cancer cells, whereas the IC_{50} values for the two nontumor-derived cell types were beyond the test range.

Table 3. Cytotoxicity of the quinoxaline derivatives against mammalian cells.[a]

Compound	IC_{50} [μg mL^{-1}]			
	L-929[b]	KB-3-1[c]	A-549[d]	HUVEC[e]
7a	>37	6	15	>37
7b	>37	20	7	>37
7c	30	18	15	4.5
7d	10	9	20	12
7e	10	9	15	6
7f	>37	5.5	20	7
7g	>37	6.5	>37	>37
7h	>37	8	4	12
7i	>37	>37	>37	>37
7j	>37	6.5	20	15
7k	20	8	20	5.5
7l	25	21	25	37

[a] Results of a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay after 5 d of incubation. [b] Mouse fibroblasts. [c] Cervix carcinoma. [d] Lung carcinoma. [e] Endothelial cells.

Conclusions

We successfully synthesized 12 new aroylquinoxaline *N*-oxides through the optimized carbene-catalyzed nucleophilic aroylation of easily accessible *O*-alkylated chloroquinoxaline *N*-oxide **5** with different aromatic aldehydes in the presence of 1,3-dimethylimidazolium iodide as the carbene precursor. To the best of our knowledge, this is the first carbene-catalyzed aroylation reaction that could be applied to the chloro nitrone unit of *N*-oxidized quinoxalines. Owing to its high substrate tolerance and use of cheap reagents, this method allows easy access to a broad range of biologically promising aroylated quinoxaline *N*-oxides. Moreover, it represents a valuable and alternative preparation procedure for such heterocycles with respect to the established Beirut reaction. The new aroylquinoxaline *N*-oxides displayed interesting specific cytotoxic effects against tumor cell lines.

Experimental Section

General Procedure for the Synthesis of Aroylated *O*-Alkylquinoxaline 1-Oxides 7a–l: 1,3-Dimethylimidazolium iodide (**6**; 36 mg, 0.159 mmol), the aldehyde (1.2 equiv.), and sodium hydride (60 wt.-% dispersion in mineral oil, 28 mg, 0.690 mmol) were added to a stirred solution of 2-chloroquinoxaline *N*-oxide (**5**; 150 mg, 0.531 mmol) in dry DMF (2 mL) at 0 °C under nitrogen. The mixture was stirred at room temperature for 30 min to 1 h. Then, water (10 mL) was added, and the organic phase was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried with sodium sulfate and then concentrated in vacuo. The residue was purified by column chromatography (30 g of silica gel; petroleum ether/ethyl acetate, 15:1) and dried in vacuo.

2-Benzoyl-3-(cyclopentyloxy)-7-fluoroquinoxaline 1-Oxide (7a): The general procedure gave **7a** as a pale yellow solid (161 mg, 0.457 mmol, 86%). M.p. 136, 261 °C (dec.). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.12 (dd, $J_{H,F}$ = 8.7 Hz, $J_{H,H}$ = 2.9 Hz, 1 H, 8-*H*), 7.90 (dd, $J_{H,H}$ = 9.2 Hz, $J_{H,F}$ = 5.1 Hz, 1 H, 5-*H*), 7.83 (dd, $J_{H,H}$ = 8.4, 1.2 Hz, 2 H, 11-*H*, 11′-*H*), 7.65–7.62 (m, 1 H, 13-*H*), 7.53 (ddd, $J_{H,H}$ = 9.2, 2.9 Hz, $J_{H,F}$ = 7.8 Hz, 1 H, 6-*H*), 7.50–7.47 (m, 2 H, 12-*H*, 12′-*H*), 5.63–5.61 (m, 1 H, 14-*H*), 1.93–1.87 (m, 2 H, 15-*H*, 15′-*H*), 1.77–1.72 (m, 2 H, 15-*H*, 15′-*H*), 1.56–1.50 (m, 4 H, 16-H_2, 16′-H_2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 186.8 (o, C9), 161.0 (o, d, $^1J_{C,F}$ = 250.9 Hz, C7), 156.5 (o, C3), 138.9 (o, C4a), 135.1 (o, C10), 134.6 (+, C13), 134.4 (o, d, $^3J_{C,F}$ = 11.0 Hz, C8a), 130.5 (o, C2), 130.0 (+, d, $^3J_{C,F}$ = 8.8 Hz, C5), 129.0 (+, 2 C, C12, C12′), 128.9 (+, 2 C, C11, C11′), 121.8 (+, d, $^2J_{C,F}$ = 24.2 Hz, C6), 104.4 (+, d, $^2J_{C,F}$ = 27.5 Hz, C8), 80.6 (+, C14), 32.6 (–, 2 C, C15, C15′), 23.5 (–, 2 C, C16, C16′) ppm. IR (ATR): $\tilde{\nu}$ = 3087, 3059, 2975, 2953, 2923, 2877, 1670 (C=O), 1619, 1597, 1589, 1559, 1503, 1451, 1438, 1432, 1413, 1397, 1360, 1333, 1326, 1318, 1307, 1290, 1233, 1192, 1178, 1163, 1136, 1122, 1090, 1073, 1034, 1026, 1001, 990, 955, 940, 921, 897, 870, 852, 828, 809, 771, 759, 710, 693, 665, 653, 607, 593, 572, 552, 528, 452, 442, 411 cm^{-1}. MS (CI): *m*/*z* (%) = 353 (3) [M + H]$^+$, 267 (5), 259 (36), 207 (3), 191 (26), 163 (100), 135 (5), 105 (17). HRMS (EI): *m*/*z* calcd. for $C_{20}H_{17}FN_2O_3$ [M]$^+$ 352.1223; found 352.1222.

Supporting Information (see footnote on the first page of this article): Further experimental details and copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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