Tetrahedron 65 (2009) 4410–4417

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The deprotonative metalation of [1,2,3]triazolo[1,5-*a*]quinoline. Synthesis of 8-haloquinolin-2-carboxaldehydes

Rafael Ballesteros-Garrido [a], Frédéric R. Leroux [a,*], Rafael Ballesteros [b,*], Belén Abarca [b,*], Françoise Colobert [a,*]

[a] *Laboratoire de stéréochimie, CNRS, Université de Strasbourg (ECPM), 25 Rue Becquerel, 67087 Strasbourg, France*
[b] *Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, Avda. Vicente Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain*

ARTICLE INFO

Article history:
Received 10 December 2008
Received in revised form 17 March 2009
Accepted 18 March 2009
Available online 27 March 2009

ABSTRACT

New highly functionalized triazoloquinolines were synthesized by applying polar organometallic methods. Double metalation and functionalization provided 3,9-dihalogenated triazoloquinolines. Ring opening of the triazole with loss of nitrogen has been performed for the first time with 3,9-dihalogenated triazoloquinolines allowing the access toward 8-haloquinolin-2-carboxaldehydes under oxidant-free conditions. This approach demonstrates that the triazole ring can be used as protecting group of 2-quinolinecarboxaldehydes, activating the C9-position for lithiation and functionalization by triazole ring opening. 8-Haloquinoline-2-carbaldehydes become in this way readily available.

1. Introduction

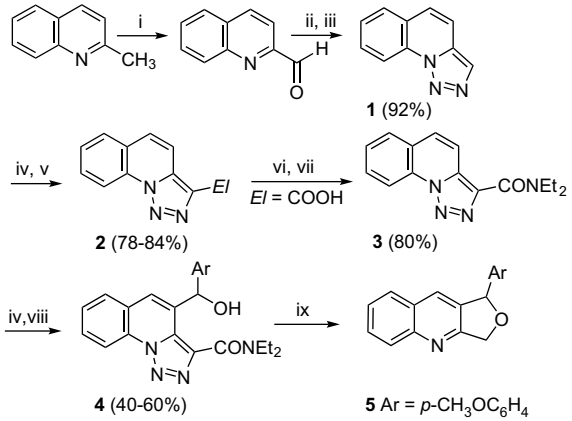
Numerous quinoline derivates, containing planar π-electron deficient polycyclic ring systems can be found in natural products[1–3] and belong to the privileged structures in pharmaceutical research.[4–9] In addition, the quinoline substructure has been efficiently incorporated in the synthesis of heterodentate P,N-ligands,[10–12] like QUINAP,[13,14] with application in asymmetric catalysis.

Many efforts were devoted to the synthesis of this heterocyclic moiety and its functionalization. The most classical methods like the Skraup[15] or Doebner–Miller synthesis[16] require drastic conditions or have low yields.

Due to our ongoing interest in the chemistry of [1,2,3]triazolo[1,5-*a*]pyridine-based heterocycles,[17–19] we focused our attention on [1,2,3]triazolo[1,5-*a*]quinolines, whose parent structure **1** is depicted in Scheme 1.

Although readily accessible, [1,2,3]triazolo[1,5-*a*]quinolines have been rarely investigated during the last 20 years.[20–22] Their functionalization afforded compounds with different functional groups on the nitrogenated ring. Strong bases like lithium di-*iso*-propylamide (LDA) undergo the deprotonative metalation[20] only at the 3-position affording compounds **2** after trapping with electrophiles (Scheme 1).[20,22] In previous works Jones and us applied this protocol to obtain the carboxamide **3**, which after subsequent remote-lithiation at the 4-position allowed the preparation of triazoloquinoline **4**. The opening of the triazole ring in the presence of acetic acid gave rise to dihydrofuro[3,4-*b*]quinoline **5**, formally a 2,3-disubstituted quinoline.[20] This methodology affords exclusively C3- and C4-disubstituted triazoloquinolines (i.e., **4**).

Comparing the reactivity of [1,2,3]triazolo[1,5-*a*]quinoline (**1**) and [1,2,3]triazolo[1,5-*a*]pyridine toward organometallic bases like LDA or BuLi, as reported by Jones and us,[23,24] a striking difference in regioselectivity can be observed. Whereas [1,2,3]triazolo[1,5-*a*]pyridine is selectively deprotonated at the 7-position, the



Scheme 1. Reagents and conditions: (i) SeO_2, dioxane. (ii) H_2NNH_2, MeOH. (iii) MnO_2, $CHCl_3$. (iv) LDA, THF −40 °C. (v) *El*-X. (vi) $SOCl_2$. (vii) $HNEt_2$. (viii) ArCHO. (ix) AcOH, heat.

* Corresponding authors. Tel.: +33390242640; fax: +33390242742.
E-mail addresses: frederic.leroux@unistra.fr (F.R. Leroux), rafael.ballesteros@uv.es (R. Ballesteros), belen.abarca@uv.es (B. Abarca), francoise.colobert@unistra.fr (F. Colobert).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.03.058

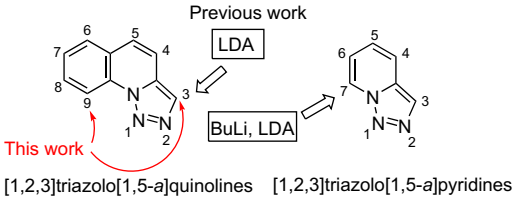


Figure 1. Metalation sites in [1,2,3]triazolo[1,5-*a*]quinolines (**1**) versus [1,2,3]triazolo[1,5-*a*]pyridines.

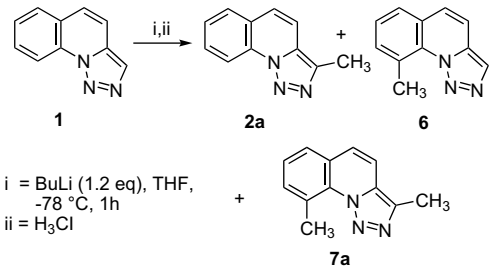
9-position in [1,2,3]triazolo[1,5-*a*]quinoline seems to be much less reactive, favoring deprotonative metalation at the 3-position, α to the ring nitrogen (Fig. 1). In contrast, this kind of C3-metalation is not observed in triazolopyridines under similar conditions. Very recently, Mongin, Quéguiner, and Abarca reported on the metalation of [1,2,3]triazolo[1,5-*a*]pyridine using magnesium- and cadmium ate complexes.[25]

In the present work, we studied the deprotonative metalation of the 9-position (*peri* position) of [1,2,3]triazolo[1,5-*a*]quinoline (**1**), as this will open route to 8-substituted quinolines.

The functionalization of quinolines at the 8-position by metalation and/or bromine/lithium exchange has been reported.[26–38] However, lack of regioselectivity is often a major drawback. Recently, Knochel et al. reported on the functionalization of quinolines via magnesiation reactions allowing after successive protection at C4 and C3, a metalation at the C8 position.[39] We decided to study the deprotonative metalation of triazoloquinolines **1** under different metalation conditions, changing the base, time, temperature, and solvent.

2. Results and discussion

We observed that the metalation of [1,2,3]triazolo[1,5-*a*]quinoline (**1**) with butyllithium in THF at −78 °C afforded after trapping with iodomethane a mixture of C3 and C9 mono- and disubstituted derivatives in a ratio **2a**/**6**/**7a**=37:32:31 and 88% conversion (Scheme 2, Table 1, entry 4).



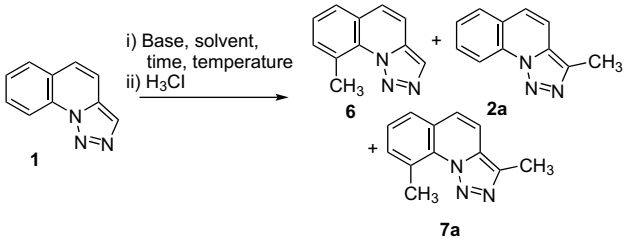
Scheme 2.

Under these conditions, the metalation was no longer regioselective at C3 as in the case of the LDA-promoted deprotonative metalation of triazoloquinoline **1**. A mixture of three metalation products was obtained, indicating that the metalation in position 9 is possible and that also a double metalation can be achieved.

We studied also the metalation of [1,2,3]triazolo[1,5-*a*]quinoline (**1**) with LiTMP in THF at −78 °C during 2 h, which resulted in a selective metalation of the 3-position.

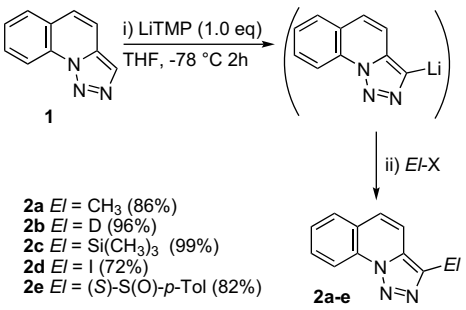
Trapping of the organolithium intermediate with iodomethane afforded compound **2a** in a yield of 86%. After deuteration with CD_3OD, triazoloquinoline **2b** was obtained in 96% yield. Chlorotrimethylsilane gave the corresponding silylated derivative **2c** in quantitative yield, iodine compound **2d** in a yield of 72% and (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate the sulfoxide **2e** in 82% yield (Scheme 3). In case of trapping with iodomethane, CD_3OD and iodine, trace amounts of disubstituted derivatives were detected in the ^{1}H NMR. Figure 2 shows the ^{1}H NMR spectra of [1,2,3]triazolo[1,5-*a*]quinoline (**1**) and the corresponding deuterated analogue **2b**.

Table 1
Metalation of [1,2,3]triazolo[1,5-*a*]quinoline (**1**) applying different bases and metalation conditions



Entry	Base[a]	Solvent	*t* (h)	*T* (°C)	**2a**[b]	**6**[b]	**7a**[b]	Conv.[b]
1	LiTMP	THF	2 h	−78 °C	91[c]	0	9	100%
2	LDA	THF	4 h	−40 °C	100[20]			84%
3	*t*-BuLi	THF	2 h	−78 °C	88	0	12	100%
4	BuLi[d]	THF	1 h	−78 °C	37	32	31	88%
5	BuLi/KO *t*-Bu	THF	2 h	−78 °C	100	0	0	59%
6	BuLi/PMDTA	THF	2 h	−78 °C	100	0	0	64%
7	BuLi	THF	2 min	−78 °C	41	50	9	82%
8	BuLi	THF	1 h	−78 °C	50	42	8	75%
9	BuLi	THF	2 h	−78 °C	54	41	5	71%
10	BuLi	THF	2 h	0 °C	100	0	0	83%
11	BuLi	Tol	2 h	0 °C	90	3	7	33%
12	BuLi[e]	THF	2 h	−78 °C	0	0	82[c]	100%

[a] Base: 1.0 equiv.
[b] Ratios determined from the integration values of the ^{1}H NMR spectra of the crude reaction mixtures.
[c] Isolated yield.
[d] BuLi: 1.2 equiv.
[e] Base (3.0 equiv) was employed.



Scheme 3.

Next, the effect of different reaction conditions (base and temperature) and solvent (THF and toluene) on the outcome of the reaction was studied (Table 1) in order to perform a selective metalation at C9.

The metalation with LiTMP and *tert*-butyllithium afforded mainly metalation at the sterically more accessible 3-position (entries 1–3) albeit with trace amounts of dimetalation products. When the Schlosser superbase (butyllithium/potassium *tert*-butoxide) was employed (entry 5), still the 3-position was exclusively metalated, however, with a decreased conversion. Almost the same result was obtained using butyllithium in presence of PMDTA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyl diethylene triamine, entry 6). Thus, amide bases and *t*-BuLi lead to an exclusive metalation at the 3-position, without any formation of 9-metalation product. The metalation at the 9-position cannot be performed with *tert*-butyllithium, probably for steric reasons. However, as the 3-Li intermediate formed under these conditions does not equilibrate with the 9-Li intermediate, we can conclude that the metalation using alkyl bases occurs under non-reversible conditions at C3.

When a slight excess of butyllithium was employed, a mixture of 3- and 9-metalation products together with a 3,9-dimetalation product was obtained in a ratio of 37:32:31 (entry 4), indicating that 9-metalation is possible.

By comparing different metalation times using butyllithium as base (now under stoichiometric conditions), a slightly higher reactivity of the 9-position could be deduced (entry 7, Table 1). The amount of dilithiated intermediate, as well as the ratio between 3- and 9-metalation remained more or less unchanged (entries 7 to 9) at −78 °C and only increased degradation was observed up to 12 h. At higher temperature (entry 10) only the metalation product at position 3 was observed.

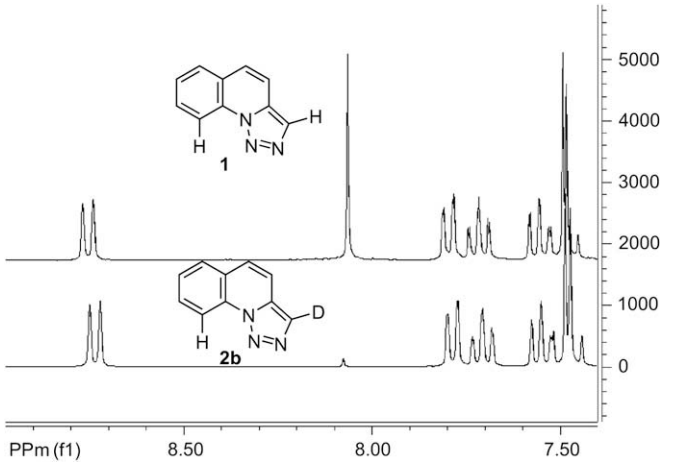
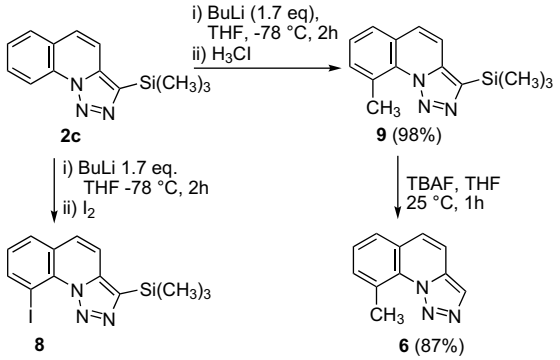


Figure 2. Metalation of triazoloquinoline **1** at C3 and trapping with CD_3OD.

So far, no base system allowed a regioselective metalation at the 9-position in order to determine if and in which way the 9-Li intermediate is converted into the 3-Li intermediate.

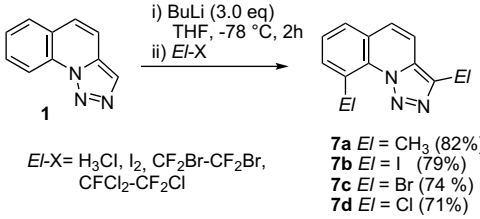
When an excess of base was used (3.0 equiv of BuLi) the dimethylated product **7a** was obtained in 82% yield after trapping with iodomethane. Although no regioselective metalation at C9 could be achieved, the double metalation undergoes in excellent yield.

In order to achieve a selective metalation at C9, the C3-position had to be protected toward metalation by means of a trimethylsilyl group. The protected triazoloquinoline **2c** could then be successfully deprotonated at C9, although an excess of butyllithium (1.7 equiv) had to be used in order to achieve complete conversion. 9-Methyl-3-(trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]quinoline (**9**) was obtained in excellent yield after trapping with iodomethane. Deprotection with tetrabutyl ammonium fluoride in THF at room temperature afforded the triazoloquinoline **6** (Scheme 4).[40] This compound was obtained in an excellent overall yield of 77% starting from quinaldine, revealing the general utility of the triazole substructure. However, when the organolithium intermediate was trapped with iodine, the iodo-derivative **8** could not be isolated in pure form, neither by crystallization nor by column chromatography, as this compound readily decomposed on silica gel.



Scheme 4.

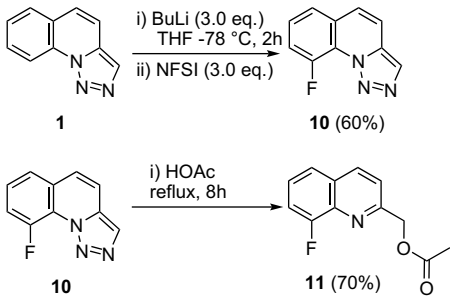
As shown in Table 1 (entry 12) a double metalation of the triazoloquinoline **1** could be achieved with an excess of butyllithium affording compounds **7a**–**d** after trapping with iodomethane, iodine, 1,2-dibromo-tetrafluoroethane, and 1,1,2-trichloro-1,2,2-trifluoroethane, respectively (Scheme 5).



Scheme 5.

Due to the increasing interest on fluorinated compounds on one side and the importance of polynitrogenated heterocycles (pyrazoles, triazoles, …) on the other for pharmaceutical and agrochemical applications,[41–46] we decided to introduce a fluorine atom onto the triazoloquinoline unit. The double metalation of triazoloquinoline **1** afforded, after trapping of the dilithiated intermediate with 3 equiv of *N*-fluorobenzenesulfonimide (NFSI, Accufluor), exclusively the monofluorinated product **10** in a yield of 60% (Scheme 6). The outcome of the reaction revealed reproducible. Even when different sources of NFSI were employed, no

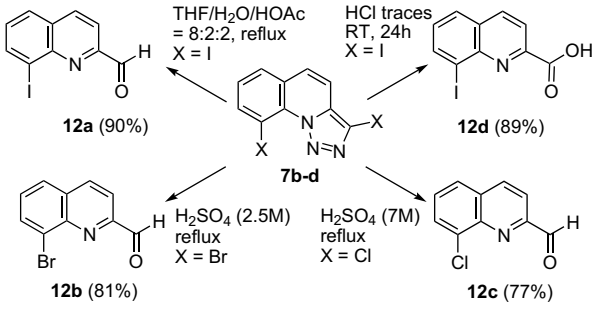
difluorinated product could be detected. Acid-mediated ring opening of the triazoloquinoline ring afforded in excellent yield the 9-fluoroquinoline **11**.



Scheme 6.

The metalation/ring opening chemistry of the triazole scaffold opens a convenient new way to 9-fluorinated triazoloquinolines and 8-fluoroquinolines. In this way, 2-(functionalized)-8-fluoroquinolines become readily accessible compared to more classical conditions.[47,48]

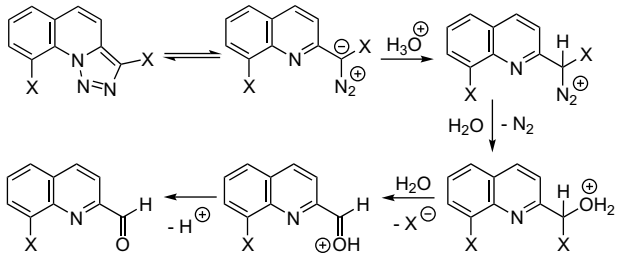
In order to study the scope and limitation of the use of 3,9-dihalogenated triazoloquinolines in the synthesis of 2,8-disubstituted quinolines, we studied more in detail their ring opening reaction. So far, no examples of ring opening reactions on *C*3-halogen-containing triazolopyridines or triazoloquinolines are described in the literature. When the triazole ring of 3,9-diiodo-[1,2,3]triazolo[1,5-*a*]quinoline (**7b**) was submitted to a ring opening reaction in a THF/water/HOAc (8:2:2) mixture at reflux, the aldehyde **12a** was obtained in a yield of 90% (Scheme 7). Another



Scheme 7.

possibility to undergo a triazole ring opening toward ketones or aldehydes frequently employed in triazolopyridine chemistry is the use of SeO_2 as oxidant. However, 3-halogenated triazoloquinolines undergo exclusively aldehyde formation. In this context, the high acid-sensitivity of 3,9-diiodo-[1,2,3]triazolo[1,5-*a*]quinoline (**7b**) has to be pointed out. We mentioned already above (Scheme 4), that 9-iodo-3-(trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]quinoline (**8**) could not be purified due to its decomposition on silica. Similarly, when 3,9-diiodo-[1,2,3]triazolo[1,5-*a*]quinoline (**7b**) was kept in an NMR tube, traces of HCl present in deuterio chloroform were sufficient to induce the ring opening affording the acid **12d** in an excellent yield (Scheme 8).

In contrast, the corresponding dibromo and dichloro derivates **7c** and **7d** underwent the ring opening only under more drastic reaction conditions. For 3,9-dibromo-[1,2,3]triazolo[1,5-*a*]quinoline (**7c**), heating under reflux in 2.5 M sulfuric acid was required to obtain the analogous quinoline **12b**. In case of 3,9-dichloro-[1,2,3]triazolo[1,5-*a*]-



Scheme 8.

quinoline (**7d**) the ring opening only occurred when 7 M sulfuric acid was employed affording quinoline **12c**.

The presumable mechanism for the ring opening reaction is similar to the one published before,[21,49,50] and is depicted in Scheme 8.

3. Conclusions

We could show, that the functionalization of [1,2,3]triazolo[1,5-*a*]quinoline by means of deprotonative metalation provides new precursors of potential pharmaceutical and biological interest. The outcome and regioselectivity of metalation reactions were studied. For the first time, *C*3-halogen-containing triazoloquinoline systems were submitted to a ring opening reaction. By this synthetic pathway, the triazole ring (which can be easily introduced by the hydrazine/MnO_2 method starting from quinoline aldehyde) has been used as protecting and activating group of 2-quinolinecarboxaldehydes providing highly substituted molecules with compatible substituent pattern toward subsequent functionalizations (Fig. 3).

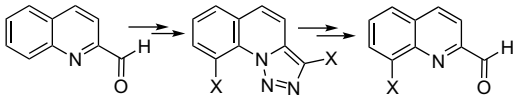


Figure 3. The triazole ring as a new protecting and 9-activating group toward 8-substituted quinolines.

4. Experimental section

4.1. General

Starting materials, if commercial, were purchased and used as such, provided that adequate checks (melting ranges, refractive indices, and gas chromatography) had confirmed the claimed purity. When known compounds had to be prepared according to literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in Schlenk tubes. They were protected by and handled under an atmosphere of argon, using appropriate glassware. Tetrahydrofuran was dried by distillation from sodium after the characteristic blue color of sodium diphenyl ketyl (benzophenone-sodium 'radical-anion') had been found to persist. Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. Melting ranges (mp) given were determined on a Kofler heated stage and found to be reproducible after recrystallization, unless stated otherwise ('decomp.'), and are uncorrected. If melting points are missing, it means all attempts to crystallize the liquid at temperatures down to −75 °C failed. Column chromatography was carried out on a column packed with silica gel 60 N spherical neutral size 63–210 μm. ^{1}H and (^{1}H decoupled) ^{13}C nuclear

magnetic resonance (NMR) spectra were recorded at 400 or 300 and 101 or 75 MHz, respectively. Chemical shifts are reported in δ units, parts per million (ppm) and were measured relative to the signals for residual chloroform (7.27 ppm). Coupling constants *J* are given in Hz. Coupling patterns are abbreviated as, for example, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), td (triplet of doublets), m (multiplet), app. s (apparent singlet), and br (broad). COSY experiments were performed for all compounds. Details regarding standard operations and abbreviations can be found in previous publications from this laboratory.[51–53]

4.2. 3-Methyl-[1,2,3]triazolo[1,5-*a*]quinoline (2a)

At 0 °C, butyllithium (3.94 mL, 5.92 mmol, 1.0 equiv) in hexanes (1.5 M) was added to a solution of 2,2,6,6-tetramethylpiperidine (0.99 mL, 0.83 g, 5.92 mmol, 1.0 equiv) in tetrahydrofuran (50.0 mL). After 15 min, the mixture was cooled to −78 °C and canulated into a solution of [1,2,3]triazolo[1,5-*a*]quinoline (**1**) (0.99 g, 5.91 mmol, 1.0 equiv) in tetrahydrofuran (75.0 mL). The mixture was kept for 2 h at −78 °C before iodomethane (0.62 mL, 1.42 g, 10.0 mmol, 1.7 equiv) was added and allowed to reach 20 °C in the course of 1 h. A saturated aqueous solution of ammonium chloride (20.0 mL) was added and the product extracted into dichloromethane (3×50.0 mL), washed with brine (10.0 mL), and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel using a gradient of ethyl acetate/cyclohexane to give 3-methyl-[1,2,3]triazolo[1,5-*a*]quinoline (**2a**) as a yellow solid (0.93 g, 86%). Mp 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (1H, d, *J* 8.0 Hz, 9-H), 7.80 (1H, dd, *J* 7.9 and 0.9 Hz, 6-H), 7.72 (1H, ddd, *J* 8.0, 7.8, and 0.9 Hz, 8-H), 7.56 (1H, dd, *J* 7.9 and 7.8 Hz, 7-H), 7.42 (2H, app. s, 5-H, 4-H), and 2.64 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136 (C), 132 (C), 129.8 (CH), 129.3 (C), 127.7 (CH), 126.5 (CH), 124.8 (CH), 123.8 (C), 115.7 (CH), 114.1 (CH), and 10.0 (CH_3); HRMS (EI) calcd for $C_{11}H_9N_3$: 183.0796, found: 183.0800. Anal. Calcd for $C_{11}H_9N_3$ (183.21): C, 71.11; H, 4.95; N, 22.94. Found: C, 71.54; H, 5.04; N, 23.04.

4.3. 3-(Deuterio)-[1,2,3]triazolo[1,5-*a*]quinoline (2b)

Prepared analogously as compound **2a** starting from [1,2,3]triazolo[1,5-*a*]quinoline (**1**) (0.49 g, 2.9 mmol, 1 equiv) and trapping of the lithiated intermediate with excess methanol-d_4 (1.00) affording 3-(deuterio)-[1,2,3]triazolo[1,5-*a*]quinoline (**2b**) as an orange solid (0.48 g, 96%). Mp 81–83 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (1H, d, *J* 8.3 Hz, 9-H), 7.76 (1H, dd, *J* 7.9 and 1.0 Hz, 6-H), 7.69 (1H, dd, *J* 8.3 and 7.7 Hz, 8-H), 7.5–7.4 (2H, m, 4-H, 7-H), and 7.44 (1H, d, *J* 9.3 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.8 (C), 131.6 (C), 130.0 (CH), 128.5 (CH), 127.3 (C, t, J_{C-D} 29.9 Hz, CD), 127.0 (CH), 126.6 (CH), 123.8 (C), 116.2 (CH), and 114.7 (CH).

4.4. 3-(Trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]quinoline (2c)

Prepared analogously as compound **2a** and trapping of the lithiated intermediate with chlorotrimethylsilane (1.26 mL, 1.09 g, 10 mmol, 1.7 equiv) affording 3-(trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]quinoline (**2c**) as an orange solid (1.37 g, 96%). Mp 99–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (1H, d, *J* 8.3 Hz, 9-H), 7.76 (1H, dd, *J* 7.9 and 1.1 Hz, 6-H), 7.69 (1H, ddd, *J* 8.3, 7.9 and 1.1 Hz, 8-H), 7.6–7.5 (2H, m, 7-H, 4-H), 7.46 (1H, d, *J* 9.3 Hz, 5-H), and 0.49 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4 (C), 136.8 (C), 132.2 (C), 129.8 (CH), 128.3 (CH), 126.8 (CH), 126.3 (CH), 123.7 (C), 116.7 (CH), 115.0 (CH), and −0.76 (3×CH_3); HRMS (EI) calcd for $C_{13}H_{15}N_3Si$: 241.1035, found: 241.1032.

4.5. 3-Iodo-[1,2,3]triazolo[1,5-*a*]quinoline (2d)

Prepared analogously as compound **2a** and trapping of the lithiated intermediate with a solution of iodine (2.41 g, 9.5 mmol, 1.6 equiv) in tetrahydrofuran (15.0 mL) affording 3-iodo-[1,2,3]triazolo[1,5-*a*]quinoline (**2d**) as a white solid (1.22 g, 70%). Mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76 (1H, d, *J* 8.3 Hz, 9-H), 7.87 (1H, dd, *J* 7.9 and 1.0 Hz, 6-H), 7.74 (1H, ddd, *J* 8.3, 7.9, and 1.0 Hz, 8-H), 7.67–7.57 (2H, m, 7-H, 4-H), and 7.41 (1H, d, *J* 9.3 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2 (C), 131.6 (C), 130.2 (CH), 128.5 (CH), 127.6 (CH), 127.4 (CH), 123.9 (C), 115.9 (CH), 114.2 (CH), and 81.7 (C); HRMS (ESI-TOF) calcd for $C_{10}H_6IN_3$ $[M+Na]^+$: 317.9499, found: 317.9458.

4.6. 3-(*p*-Tolylsulfinyl)-[1,2,3]triazolo[1,5-*a*]quinoline (2e)

Prepared analogously as compound **2a** and trapping of the lithiated intermediate by addition into a solution of (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate (2.21 g, 7.40 mmol, 1.3 equiv) in tetrahydrofuran (50.0 mL) at −45 °C. Usual workup and purification by flash chromatography on silica gel using a gradient of ethyl acetate/cyclohexane (from 1:3 to 1:1) afforded 3-(*p*-tolylsulfinyl)-[1,2,3]triazolo[1,5-*a*]quinoline (**2e**) as a white solid (1.49 g, 82%). Mp 145–147 °C; $[\alpha]_D^{22}$ +104.2 (*c* 1, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (1H, d, *J* 8.4 Hz, 9-H), 7.87 (1H, dd, *J* 7.9 and 1.0 Hz, 6-H), 7.81 (1H, ddd, *J* 8.4, 7.3, and 1.2 Hz, 8-H), 7.71 (3H, m, 2′-H(*p*-Tol), 4-H), 7.63 (2H, m, 7-H, 5-H), 7.32 (2H, d, *J* 8.0 Hz, 3′-H(*p*-Tol)), and 2.39 (3H, s, CH_3 (*p*-Tol)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4 (C), 141.7 (C), 140.3 (C), 131.7 (C), 131.1 (C), 130.7 (CH), 130.1 (2×CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 124.6 (2×CH), 124.0 (C), 116.4 (CH), 114.4 (CH), and 21.4 (CH_3); HRMS (EI) calcd for $C_{17}H_{13}N_3OS$: 307.0779, found: 307.0784.

4.7. 9-Methyl-[1,2,3]triazolo[1,5-*a*]quinoline (6)

At 25 °C, tetrabutylammonium fluoride (1.20 mL, 1.20 mmol, 1.9 equiv) in tetrahydrofuran (1 M) was added to a solution of 9-methyl-3-(trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]quinoline (**9**) (0.15 g, 0.60 mmol, 1.0 equiv) in tetrahydrofuran (15.0 mL). After 1 h at 25 °C, a saturated aqueous solution of sodium chloride (20.0 mL) was added. The product was extracted into dichloromethane (3×50 mL), washed with brine (10.0 mL) and dried over Na_2SO_4. Flash chromatography on silica gel using a mixture of ethyl acetate/cyclohexane (2:3) gave 9-methyl-[1,2,3]triazolo-[1,5-*a*]quinoline (**6**) as a colorless solid (0.10 g, 92%). Mp 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (1H, s, 3-H), 7.60 (1H, d, *J* 7.7 Hz, 6-H), 7.50 (1H, d, *J* 7.2 Hz, 8-H), 7.5–7.4 (3H, m, 7-H, 5-H, 4-H), and 3.16 (3H, s, 9-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.9 (CH), 132.7 (C), 131.6 (C), 129.5 (C), 127.6 (CH), 126.3 (CH), 126.2 (CH), 126.0 (CH), 125.2 (C), 114.2 (CH), and 24.3 (CH_3); HRMS (EI) calcd for $C_{11}H_9N_3$: 183.0796, found: 183.0791.

4.8. 3,9-Dimethyl-[1,2,3]triazolo[1,5-*a*]quinoline (7a)

At −78 °C, butyllithium (2.36 mL, 3.54 mmol, 3.0 equiv) in hexanes (1.5 M) was added to a solution of [1,2,3]triazolo[1,5-*a*]quinoline (**1**) (0.19 g, 1.18 mmol, 1.0 equiv) in tetrahydrofuran (15.0 mL). After 2 h at −78 °C, iodomethane (0.24 mL, 0.54 g, 3.8 mmol, 3.2 equiv) was added and allowed to reach 20 °C in the course of 1 h. A saturated aqueous solution of ammonium chloride (20.0 mL) was added and the product extracted into dichloromethane (3×50.0 mL), washed with brine (10.0 mL), and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel using a 1:1 mixture of ethyl acetate/cyclohexane as eluent, which provided 3,9-dimethyl-[1,2,3]triazolo[1,5-*a*]quinoline **7a** as a yellow solid (0.19 g, 82%). Mp 84–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (1H, dd, *J* 7.7 and 0.9 Hz, 6-H), 7.51 (1H, dd, *J* 7.4 and

0.9 Hz, 8-H), 7.43 (1H, dd, *J* 7.7 and 7.4 Hz, 7-H), 7.38 (2H, app. s, 4-H, 5-H), 3.18 (3H, s, 9-CH_3), and 2.63 (3H, s, 3-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.7 (C), 132.8 (CH), 131.9 (C), 130.4 (C), 129.6 (C), 126.4 (CH), 126.3 (CH), 126.2 (CH), 125.5 (C), 114.1 (CH), 24.4 (9-CH_3), and 10.2 (3-CH_3); HRMS (EI) calcd for $C_{12}H_{11}N_3$: 197.0952, found: 197.0949. Anal. Calcd for $C_{12}H_{11}N_3$ (197.24): C, 73.07; H, 5.62; N, 21.30. Found: C, 72.65; H, 5.71; N, 21.48.

4.9. 3,9-Diiodo-[1,2,3]triazolo[1,5-*a*]quinoline (7b)

Prepared analogously as compound **7a** starting from [1,2,3]triazolo[1,5-*a*]quinoline (**1**) (0.99 g, 5.9 mmol, 1.0 equiv) and trapping of the lithiated intermediate with a solution of iodine (6.09 g, 24 mmol, 4.0 equiv). Crystallization from dichloromethane gave 3,9-diiodo-[1,2,3]triazolo[1,5-*a*]quinoline (**7b**) as pale yellow needles (2.06 g, 82%). Decomp. 144 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (1H, dd, *J* 7.7 and 1.3 Hz, 6-H), 7.83 (1H, dd, *J* 7.8 and 1.3 Hz, 8-H), 7.52 (1H, d, *J* 9.3 Hz, 4-H), 7.46 (1H, d, *J* 9.3 Hz, 5-H), and 7.25 (1H, dd, *J* 7.7 and 7.8 Hz, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0 (CH), 134.8 (C), 133.4 (C), 129.2 (CH), 128.3 (CH), 127.9 (CH), 126.7 (2×C), 115.2 (CH), and 83.2 (C); HRMS (EI) calcd for $C_{10}H_5I_2N_3$: 420.8573, found: 420.8567. Anal. Calcd for $C_{10}H_5I_2N_3$ (426.02): C, 28.53; H, 1.23; N, 9.98. Found: C, 28.00; H, 1.26; N, 9.98.

4.10. 3,9-Dibromo-[1,2,3]triazolo[1,5-*a*]quinoline (7c)

Prepared analogously as compound **7a** starting from [1,2,3]triazolo[1,5-*a*]quinoline (**1**) (0.44 g, 2.6 mmol, 1.0 equiv) followed by addition of 1,2-dibromo-1,1,2,2-tetrafluoroethane (2.70 g, 10.4 mmol, 4.0 equiv) affording after crystallization from dichloromethane/hexanes 3,9-dibromo-[1,2,3]triazolo[1,5-*a*]quinoline (**7c**) as pale brown needles (0.62 g, 74%). Mp 166–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (1H, dd, *J* 7.8 and 1.3 Hz, 6-H), 7.79 (1H, dd, *J* 7.9 and 1.3 Hz, 8-H), 7.53 (1H, d, *J* 9.3 Hz, 4-H), 7.47 (1H, d, *J* 9.3 Hz, 5-H), and 7.42 (1H, dd, *J* 7.9 and 7.8 Hz, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.3 (CH), 131.4 (C), 130.8 (C), 128.4 (CH), 128.0 (CH), 127.7 (CH), 127.2 (C), 114.5 (CH), 114.4 (C), and 110.3 (C); HRMS (ESI-TOF) calcd for $C_{10}H_5^{79}Br_2N_3$ $[M+Na]^+$: 347.8742, found: 347.8719; calcd for $C_{10}H_5^{79}Br^{81}BrN_3$ $[M+Na]^+$: 349.8722, found: 349.8296; calcd for $C_{10}H_5^{81}Br_2N_3$ $[M+Na]^+$: 351.8703, found: 351.8684. Anal. Calcd for $C_{10}H_5Br_2N_3$ (326.97): C, 36.73; H, 1.54; N, 12.85. Found: C, 36.24; H, 1.67; N, 12.64.

4.11. 3,9-Dichloro-[1,2,3]triazolo[1,5-*a*]quinoline (7d)

Prepared analogously as compound **7a** starting from [1,2,3]triazolo[1,5-*a*]quinoline (**1**) (0.43 g, 2.6 mmol, 1.0 equiv) and trapping of the lithiated intermediate with 1,1,2-trichloro-1,2,2-trifluoroethane (1.24 mL, 1.94 g, 10.4 mmol, 4.0 equiv). After crystallization from cold dichloromethane/hexane 3,9-chloro-[1,2,3]triazolo[1,5-*a*]quinoline (**7d**) was obtained as pale brown needles (0.43 g, 71%). Mp 169–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (1H, d, *J* 7.9 and 1.1 Hz, 6-H), 7.71 (1H, dd, *J* 7.9 and 1.1 Hz, 8-H), and 7.5–7.4 (3H, m, 7-H, 4-H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.3 (CH), 129.4 (C), 129.1 (C), 127.8 (C), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.9 (C), 123.9 (C), and 113.9 (CH); HRMS (ESI-TOF) calcd for $C_{10}H_5^{35}Cl_2N_3$ $[M+Na]^+$: 259.9753, found: 259.9774; calcd for $C_{10}H_5^{35}Cl^{37}ClN_3$ $[M+Na]^+$: 261.9724, found: 261.9748; calcd for $C_{10}H_5^{37}Cl_2N_3$ $[M+Na]^+$: 263.9697, found: 263.9736. Anal. calcd for $C_{10}H_5Cl_2N_3$ (238.07): C, 50.45; H, 2.12; N, 17.63. Found: C, 50.20; H, 2.37; N, 17.22.

4.12. 9-Iodo-3-(trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]-quinoline (8)

At −78 °C, butyllithium (0.90 mL, 1.40 mmol, 1.7 equiv) in hexanes (1.5 M) was added to a solution of 3-(trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]quinoline (**2c**) (0.19 g, 0.80 mmol, 1.0 equiv) in tetrahydrofuran (15.0 mL). After 2 h at −78 °C, iodine (0.24 g, 0.96 mmol, 1.2 equiv) in THF (5.0 mL) was added and the mixture allowed to reach 20 °C. The product was characterized by HRMS as the product degrades during purification. HRMS (EI) calcd for $C_{13}H_{14}IN_3Si$: 367.0001, found: 366.9999.

4.13. 9-Methyl-3-(trimethylsilyl)-[1,2,3]triazolo-[1,5-*a*]quinoline (9)

Prepared analogously as compound **8** starting from 3-(trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]quinoline (**2c**) (0.19 g, 0.8 mmol, 1.0 equiv) followed by addition of iodomethane (0.11 mL, 1.76 g, 1.7 mmol, 1.2 equiv). A saturated aqueous solution of ammonium chloride (20.0 mL) was added followed by extraction into dichloromethane (3×50.0 mL). The combined organic extracts were washed with brine (10.0 mL) and dried over Na_2SO_4 affording 3-(trimethylsilyl)-[1,2,3]triazolo[1,5-*a*]quinoline (**9**) as yellow solid 0.20 g (99%). Mp 106–108 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* 8.1 Hz, 6-H), 7.6–7.5 (2H, m), 7.5–7.4 (2H, m), 3.21 (3H, s, CH_3), and 0.49 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9 (C), 137.7 (C), 132.9 (CH), 132.1 (C), 129.8 (C), 127.6 (CH), 126.3 (CH), 126.2 (CH), 125 .3 (C), 115.5 (CH), 24.6 (CH_3), and −0.81 (3×CH_3); HRMS (EI) calcd for $C_{14}H_{17}N_3Si$: 255.1191, found: 255.1201.

4.14. 9-Fluoro-[1,2,3]triazolo[1,5-*a*]quinoline (10)

At −78 °C, butyllithium (2.33 mL, 3.50 mmol, 3.0 equiv) in hexanes (1.5 M) was added to a solution of [1,2,3]triazolo[1,5-*a*]quinoline (**1**) (0.20 g, 1.20 mmol, 1.0 equiv) in tetrahydrofuran (15.0 mL). After 2 h at −78 °C, a solution of *N*-fluorodibenzenesulfonimide (1.01 g, 3.50 mmol, 3.0 equiv) in tetrahydrofuran (20.0 mL) was added and allowed to reach 20 °C during 1 h. After addition of a saturated aqueous solution of ammonium chloride (50.0 mL), the product was extracted into ethyl acetate (3×50.0 mL), washed with brine (10.0 mL), and dried over Na_2SO_4. Flash chromatography over silica gel using a 1:1 mixture of ethyl acetate/cyclohexane afforded 9-fluoro-[1,2,3]triazolo[1,5-*a*]quinoline (**10**) as a brown solid (0.14 g, 60%). Mp 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (1H, d, J_{F-H} 0.4 Hz, 3-H) and 7.6–7.4 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.8 (d, J_{F-C} 259.5 Hz, 9-C), 132.4 (s, 2×C), 127.1 (d, J_{F-C} 7.6 Hz, CH), 126.8 (d, J_{F-C} 1.5 Hz, C), 126.6 (d, J_{F-C} 1.3 Hz, CH), 126.5 (d, J_{F-C} 2.2 Hz, CH), 124.0 (d, J_{F-C} 4.2 Hz, CH), 117.1 (d, J_{F-C} 19.5 Hz, CH), and 115.8 (d, J_{F-C} 1.5 Hz, CH); HRMS (ESI-TOF) calcd for $C_{10}H_6FN_3$ $[M+Na]^+$: 210.0438, found: 210.0440.

4.15. (8-Fluoroquinolin-2-yl)methyl acetate (11)

A solution of 9-fluoro-[1,2,3]triazolo[1,5-*a*]quinoline (18.7 mg, 0.100 mmol, 1 equiv) in acetic acid (15.0 mL) was heated under reflux during 8 h. After cooling to room temperature, excess acetic acid was distilled off and the residue neutralized with a saturated aqueous solution of sodium hydrogen carbonate (5.00 mL). The aqueous phase was extracted with dichloromethane (3×10.0 mL), washed with brine (10.0 mL), and dried over Na_2SO_4. The product was purified by flash chromatography on silica gel using a 1:1 mixture of ethyl acetate/cyclohexane as eluent, which provided (8-fluoroquinolin-2-yl)methyl acetate **11** as a colorless oil (15.3 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (1H, dd, *J* 8.6 and 1.5 Hz, 4-H), 7.54 (1H, d, *J* 8.0 Hz, 5-H), 7.41 (1H, d, *J* 8.6 Hz, 3-H), 7.4–7.3 (2H, m, 6-H, 7-H), 5.38 (2H, s, CH_2), and 2.13 (3H, d, *J* 3.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (COO), 157.9 (d, J_{F-C} 256.9 Hz, 8-C), 156.7 (d, J_{F-C} 1.5 Hz, C), 137.9 (d, J_{F-C} 11.7 Hz, C), 136.7 (d, J_{F-C} 3.1 Hz, CH), 129.4 (d, J_{F-C} 2.2 Hz, C), 126.5 (d, J_{F-C} 8.0 Hz, CH), 123.3 (d, J_{F-C} 4.7 Hz, CH), 120.3 (CH), 113.9 (d, J_{F-C} 19.0 Hz, CH), 67.3 (CH_2), and

20.9 (CH_3); HRMS (ESI-TOF) calcd for $C_{12}H_{10}FNO_2$ $[M+Na]^+$: 242.0588, found: 242.0554.

4.16. 8-Iodoquinoline-2-carbaldehyde (12a)

3,9-Diiodo-[1,2,3]triazolo[1,5-*a*]quinoline (**7b**) (0.13 g, 0.30 mmol, 1.0 equiv) was diluted in a mixture of water (8.00 mL), tetrahydrofuran (2.00 mL), and acetic acid (2.00 mL), and heated to reflux. The reaction, becoming deep red when the reagent was completely consumed, was monitored by TLC. Upon completion of the reaction (4 h), acetic acid was separated by distillation and the reaction mixture was quenched with a saturated aqueous solution of sodium thiosulphate (20.0 mL), observing the disappearance of the red coloration. The mixture was treated with a saturated aqueous solution of sodium hydrogen carbonate (5.0 mL) until pH 8 and the product extracted into dichloromethane (3×50.0 mL). The organic layers were combined, washed with brine (20.0 mL), and dried over Na_2SO_4. Flash column chromatography on silica gel using a gradient ethyl acetate/cyclohexane (1:5 to 2:1) gave 8-iodoquinoline-2-carbaldehyde (**12a**) as a yellow solid (76.4 mg, 90%). Mp 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.30 (1H, s, CHO), 8.44 (1H, dd, *J* 7.4 and 1.2 Hz, 5-H), 8.25 (1H, d, *J* 8.4 Hz, 3-H), 8.05 (1H, d, *J* 8.4 Hz, 4-H), 7.89 (1H, dd, *J* 8.2 and 1.2 Hz, 7-H), and 7.39 (1H, dd, *J* 8.2 and 7.4 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4 (CH), 153.4 (C), 146.8 (C), 141.2 (CH), 138.3 (CH), 130.7 (C), 130.1 (CH), 128.7 (CH), 118.1 (CH), and 104.8 (C); HRMS (ESI-TOF) calcd for $C_{10}H_6INO$ $[M+Li]^+$: 289.9649, found: 289.9640. Anal. Calcd for $C_{10}H_6INO$ (283.07): C, 42.30; H, 2.14; N, 4.830. Found: C, 42.30; H, 2.43; N, 4.83.

4.17. 8-Bromoquinoline-2-carbaldehyde (12b)

3,9-Dibromo-[1,2,3]triazolo[1,5-*a*]quinoline (**7c**) (98.1 mg, 0.30 mmol, 1.0 equiv) was diluted in aqueous sulfuric acid (10.0 mL, 2.5 M) and heated to reflux. The reaction was monitored by TLC. Upon completion of the reaction (6 h) a saturated aqueous solution of sodium hydrogen carbonate (5.0 mL) was added until pH 8. The resulting mixture was extracted with dichloromethane (3×50.0 mL), washed with brine (20.0 mL), and dried over Na_2SO_4. Flash column chromatography on silica gel using a gradient ethyl acetate/cyclohexane (1:5 to 2:1) gave 8-bromoquinoline-2-carbaldehyde (**12b**) as a yellow solid (57.4 mg, 81%). Mp 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.30 (1H, s, CHO), 8.32 (1H, d, *J* 8.3 Hz, 3-H), 8.15 (1H, d, *J* 7.5 Hz, 5-H), 8.08 (1H, d, *J* 8.3 Hz, 4-H), 7.87 (1H, d, *J* 8.3 Hz, 7-H), and 7.53 (1H, dd, *J* 8.3 and 7.5 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4 (CH), 153.1 (C), 145.0 (C), 138.1 (CH), 134.2 (CH), 131.3 (C), 129.4 (CH), 127.7 (CH), 126.1 (C), and 118.0 (CH); HRMS (ESI-TOF) calcd for $C_{10}H_6^{79}BrNO$ $[M+Li]^+$: 241.9788, found: 241.9756; calcd for $C_{10}H_6^{81}BrNO$ $[M+Li]^+$: 243.9768, found: 243.9736.

4.18. 8-Chloroquinoline-2-carbaldehyde (12c)

3,9-Dichloro-[1,2,3]triazolo[1,5-*a*]quinoline (**7d**) (0.14 g, 0.6 mmol, 1.0 equiv) was diluted in aqueous sulfuric acid (15.0 mL, 7 M) and heated to reflux. The reaction was monitored by TLC. Upon completion of the reaction (24 h), a saturated aqueous solution of sodium hydrogen carbonate (5.0 mL) was added until pH 8. The resulting mixture was extracted with dichloromethane (3×50.0 mL), the organic extracts washed with brine (20.0 mL) and dried over Na_2SO_4. Flash column chromatography on silica gel using a gradient ethyl acetate/cyclohexane (1:5 to 2:1) gave 8-chloroquinoline-2-carbaldehyde (**12c**) as a yellow solid (88 mg, 77%). Mp 129–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.32 (1H, s, CHO), 8.35 (1H, d, *J* 8.4 Hz, 3-H), 8.11 (1H, d, *J* 8.4 Hz, 4-H), 7.95 (1H, dd, *J* 7.5 and 1.3 Hz, 5-H), 7.84 (1H, dd, *J* 8.2 and 1.3 Hz, 7-H), and 7.62 (1H, dd, *J* 8.2 and 7.5 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4 (CHO), 152.9 (C), 144.3 (C), 137.9 (CH), 134.9 (C), 131.4 (C), 130.6 (CH), 129.1 (CH), 126.9 (CH), and 118.1 (CH); HRMS (ESI-TOF) calcd for $C_{10}H_6^{35}ClNO$ $[M+Li]^+$: 198.0293, found: 198.0297; calcd for $C_{10}H_6^{37}ClNO$ $[M+Li]^+$: 200.0276, found: 200.0265.

4.19. 8-Iodoquinoline-2-carboxylic acid (12d)

In a NMR tube 3,9-diiodo-[1,2,3]triazolo[1,5-*a*]quinoline (**7c**) (13 mg, 0.03 mmol, 1.0 equiv) was dissolved in [^{2}H]chloroform (0.7 mL) affording a pink coloration becoming deep purple after 24 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.34 (1H, br s, COOH), 8.46 (1H, dd, *J* 7.4 and 1.20 Hz, 5-H), 8.40 (1H, d, *J* 8.4 Hz, 3-H), 8.32 (1H, d, *J* 8.4 Hz, 4-H), 7.95 (1H, dd, *J* 8.2 and 1.2 Hz, 7-H), and 7.45 (1H, dd, *J* 8.2, 7.4 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (C), 146.6 (C), 144.8 (C), 142.5 (CH), 139.9 (CH), 130.3 (CH,C), 128.6 (CH), 120.1 (CH), and 103.0 (C); HRMS (ESI-TOF) calcd for $C_{10}H_6INO_2$ $[M+Na]^+$: 321.9335, found: 321.9312.

Acknowledgements

This work was financially supported by the the Ministère de la Recherche (France), the Ministerio de Educación y Ciencia (Spain) (Project CTQ2006-15672-C05-03), the CNRS (France). R.B.-G. is much indebted to the Ministère de l'Éducation Nationale, de la Recherche et de la Technologie (France) for a doctoral fellowship.

References and notes

1. Morimoto, Y.; Matsuda, F.; Shirahama, H. *Synlett* **1991**, 201–203.
2. Isobe, M.; Nishikawa, T.; Yamamoto, N.; Tsukiyama, T.; Ino, A.; Okita, T. *J. Heterocycl. Chem.* **1992**, *29*, 619–625.
3. Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605–618.
4. Markees, D. G.; Dewey, V. C.; Kidder, G. W. *J. Med. Chem.* **1970**, *13*, 324–326.
5. Campbell, S. F.; Hardstone, J. D.; Palmer, M. J. *J. Med. Chem.* **1988**, *31*, 1031–1035.
6. Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274–5293.
7. Elliott, J. M.; Carling, R. W.; Chambers, M.; Chicchi, G. G.; Hutson, P. H.; Jones, A. B.; MacLeod, A.; Marwood, R.; Meneses-Lorente, G.; Mezzogori, E.; Murray, F.; Rigby, M.; Royo, I.; Russell, M. G. N.; Sohal, B.; Tsao, K. L.; Williams, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5748–5751.
8. Duffour, J.; Gourgou, S.; Desseigne, F.; Debrigode, C.; Mineur, L.; Pinguet, F.; Poujol, S.; Chalbos, P.; Bressole, F.; Ychou, M. *Cancer Chemother. Pharmacol.* **2007**, *60*, 383–389.
9. Alhaider, A. A.; Abdelkader, M. A.; Lien, E. J. *J. Med. Chem.* **1985**, *28*, 1394–1398.
10. Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497–537.
11. Chelucci, G.; Orru, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471–9515.
12. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.
13. Alcock, N. W.; Hulmes, D. I.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 395–397.
14. Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743–756.
15. Manske, R. H. F.; Kulka, M. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, NY, 1953; pp 59–98.
16. von Miller, W.; Doebner, O. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2464–2472.
17. Abarca, B.; Ballesteros, R.; Ballesteros-Garrido, R.; Colobert, F.; Leroux, F. R. *Tetrahedron* **2008**, *64*, 3794–3801.
18. Abarca, B.; Ballesteros, R.; Ballesteros-Garrido, R.; Colobert, F.; Leroux, F. R. *Tetrahedron* **2007**, *63*, 10479–10485.
19. Colobert, F.; Ballesteros-Garrido, R.; Leroux, F. R.; Ballesteros, R.; Abarca, B. *Tetrahedron Lett.* **2007**, *48*, 6896–6899.
20. Abarca, B.; Ballesteros, R.; Gomez-Aldaravi, E.; Jones, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1897–1901.
21. Jones, G.; Mouat, D. J.; Tonkinson, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2719–2723.
22. Abarca, B.; Gomez-Aldaravi, E.; Jones, G. *J. Chem. Res., Synop.* **1984**, 140–141.
23. Jones, G.; Sliskovic, D. R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 967–971.
24. Abarca, B.; Ballesteros, R.; Elmasnaouy, M. *Tetrahedron* **1998**, *54*, 15287–15292.
25. Bentabed-Ababsa, G.; Blanco, F.; Derdour, A.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Ballesteros, R.; Abarca, B. *J. Org. Chem.* **2008**. doi:10.1021/jo801675h
26. Comins, D. L.; Nolan, J. M.; Bori, I. D. *Tetrahedron Lett.* **2005**, *46*, 6697–6699.
27. Mongin, F.; Queguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090.
28. Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120–5121.
29. Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1999**, *55*, 12149–12156.
30. Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376–393.
31. Dumouchel, S.; Mongin, F.; Trecourt, F.; Queguiner, G. *Tetrahedron Lett.* **2003**, *44*, 2033–2035.

32. Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481–2483.
33. Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 1008–1013.
34. Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 54–63.
35. Lefebvre, O.; Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 2115–2121.
36. Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 1576–1588.
37. Schlosser, M.; Marull, M. *Eur. J. Org. Chem.* **2003**, 1569–1575.
38. Cottet, F.; Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 1559–1568.
39. Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett.* **2007**, *9*, 5525–5528.
40. Yu, S.; Keay, B. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2600–2601.
41. Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, NY, 1994.
42. Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992–1012.
43. Jeschke, P.; Baston, E.; Leroux, F. R. *Mini-Rev. Med. Chem.* **2007**, *7*, 1027–1034.
44. Leroux, F. *Curr. Med. Chem.* **2005**, *12*, 1623–1629.
45. *Bioorganic and Medicinal Chemistry of Fluorine*; Begue, J. P., Bonnet-Delpon, D., Eds.; John Wiley & Sons: Hoboken, New Jersey, NJ, 2008.
46. Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305–321.
47. Chambers, R. D.; Holling, D.; Sandford, G.; Batsanov, A. S.; Howard, J. A. K. *J. Fluorine Chem.* **2004**, *125*, 661–671.
48. Chambers, R. D.; Holling, D.; Sandford, G.; Puschmann, H.; Howard, J. A. K. *J. Fluorine Chem.* **2002**, *117*, 99–101.
49. Jones, G.; Sliskovic, R.; Foster, B.; Rogers, J.; Smith, A. K.; Wong, M. I.; Yarham, A. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 78–81.
50. Abarca, B.; Ballesteros, R.; Rodrigo, G.; Jones, G.; Veciana, J.; Vidal-Gancedo, J. *Tetrahedron* **1998**, *54*, 9785–9790.
51. Leroux, F. R.; Bonnafoux, L.; Heiss, C.; Colobert, F.; Lanfranchi, D. A. *Adv. Synth. Catal.* **2007**, *349*, 2705–2713.
52. Leroux, F.; Mettler, H. *Adv. Synth. Catal.* **2007**, *349*, 323–336.
53. Leroux, F.; Hutschenreuter, T. U.; Charriere, C.; Scopelliti, R.; Hartmann, R. W. *Helv. Chim. Acta* **2003**, *86*, 2671–2686.