Regiospecific nucleophilic substitution of fluorine in fused tetrafluoroquinolines with *N*- and *O*-nucleophiles.

J. Chem. Research (S), 2002, 357–358
J. Chem. Research (M), 2002, 0829–0840

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5,6,7,8-Tetrafluoro-1,2-azolo[3,4-*b*;4′,3′-*e*]quinolines react regiospecifically with aliphatic and aromatic amines, alcohols and phenols yielding 7-substituted 5,6,8-trifluoro-1,2-azolo[3,4-*b*;4′,3′-*e*]quinolines.

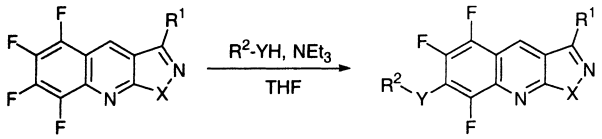
Keywords: regiospecific nucleophilic substitution of fluorine

It has been shown in the literature that substituted bispyrazolo[3,4-*b*;4′,3′-*e*]pyridines have antibacterial properties. Because of their large conjugated π-systems, they are highly fluorescent and of potential use in photophysical processes and devices, such as photo-induced transfer reactions, pyrazole-based electroluminescent compounds and polymers. Usually, bispyrazolo[3,4-*b*;4′,3′-*e*]pyridines are synthesised by condensation of aromatic or heterocyclic aldehydes with 5-amino-1,2-azoles. With *ortho*-halosubstituted aldehydes either a [2+1] or [1+1]cyclocondensation can occur.[3] The same [1+1] reaction of benzaldehydes with aromatic amines gives substituted acridines. In our earlier publication,[3] we have shown that such fused azoloquinolines are highly fluorescent. Therefore, we wanted to study nucleophilic substitution in these compounds to evaluate them as fluorescent labels.

We wish to report here that 5,6,7,8-tetrafluoro-1,2-azolo[3,4-*b*;4′,3′-*e*]quinolines[3] **1–7** smoothly react with aliphatic and aromatic amines, alcohols and phenols in the presence of the appropriate base (Table 1). Nucleophilic substitution occurs regiospecifically at the 7- position resulting in *N*- and *O*-derivatives of 5,6,8-trifluoro-1,2-azolo[3,4-*b*;4′,3′-*e*]quinolines **8–24** in high yield. Thus, primary and secondary aliphatic amines react with quinolines **1–7** in tetrahydrofuran, using triethylamine or excess of the corresponding amine to neutralise the acid generated. The reaction was complete after 3–10 days at room temperature. However, it is more convenient to carry out the reaction in tetrahydrofuran at reflux. In this case, the formation of 7-*N*-substituted trifluoroquinolines **8–10**, **12–14**, **16–21** is complete after 3–12 h in 72–97 % yield. Indoles substitute fluorine only in the presence of potassium carbonate as the base, affording derivatives **11** and **17**. *p*-Hexylaniline reacts only with **7** when *t*-BuLi is used to prepare the corresponding, more reactive anilide intermediate. It is very interesting that **7** and 5-amino-3-*t*-butyl-1-methyl-1,2-pyrazole, with the sodium hydride/dimethylformamide system, forms the *bis*-substituted aminopyrazole **24**. Apparently, the monosubstituted derivative is a better nucleophile than the aminopyrazole itself. The formation of **24** is the only case where we have seen such *bis*-arylation.

Phenols react with tetrafluoroquinolines **5**,**7** while using the system potassium carbonate/dimethylformamide at 60–80°C, with regiospecific formation of 7-*O*-substituted trifluoroquinolines **15**, **22**, **23** in 62–77 % yield. Aliphatic alcohols

Table 1 Nucleophilic substitution in fused tetrafluoroquinolines with *N*- and *O*-nucleophiles



1-7 **8-23**

Reactant	Product	X	R^1	R^2Y	Yield, %
1	**8**	NMe	Me	4-methylpiperazin-1-yl	83
2	**9**	NMe	***t*-Bu**	Me_2N	75
"	**10**	"	"	2-$MeOC_6H_4CH_2NH$	81
"	**11**	"	"	3-hydroxymethylindol-1-yl	35[a]
3	**12**	NMe	Ph	2-$MeOC_6H_4CH_2NH$	85
4	**13**	NPh	Me	4-methylpiperazin-1-yl	97
5	**14**	NPh	Ph	2-$MeOC_6H_4CH_2NH$	72
"	**15**	"	"	coumarin-7-oxy	77[a]
6	**16**	O	Me	(*R*)-(+)-PhCH(Me)NH	75
"	**17**	"	"	5-nitroindol-1-yl	90[a]
7	**18**	S	Me	Me_2N	64
"	**19**	"	"	2-$MeOC_6H_4CH_2NH$	83
"	**20**	"	"	(*R*)-(+)-PhCH(Me)NH	85
"	**21**	"	"	4-$C_6H_{13}C_6H_4NH$	67[b]
"	**22**	"	"	(*S*)-(-)-2-methylbutoxy	62[c]
	23	"	"	4-methylcoumarin-7-oxy	65[a]

[a] K_2CO_3, DMF, 60-80°C. [b] *t*-BuLi, THF. [c] NaH, DMF

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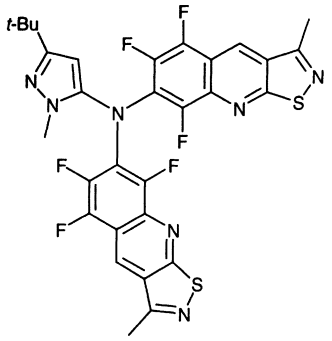

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Figure 1

substitute compound **7** only when sodium hydride is used as the base, in dimethylformamide as the solvent.

All yields refer to products isolated by crystallisation and/or column chromatography. The compounds obtained were fully characterised by MS, ^{1}H NMR, ^{13}C NMR spectral techniques. The seven-substitution is derived unambiguously from the coupling pattern in the ^{13}C NMR spectrum. In all cases, the C-8 of the azoloquinoline has no $^{2}J_{CF}$ coupling.

In conclusion, we have found that smooth, base catalysed conditions can be found for the nucleophilic substitution of fluorine in 5,6,7,8-tetrafluoro-1,2-azolo[3,4-*b*;4´,3´-*e*]quinolines with aliphatic and aromatic amines, phenols and alcohols, which is regiospecific at the *7*-position.

Techniques used: ^{1}H and ^{13}C NMR, MSEI. (data on all new compounds)

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Received 4 February 2002; accepted 11 June 2002
Paper 02/1230

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