Synthesis of fluorine-substituted anthraquinones and aza-anthraquinones

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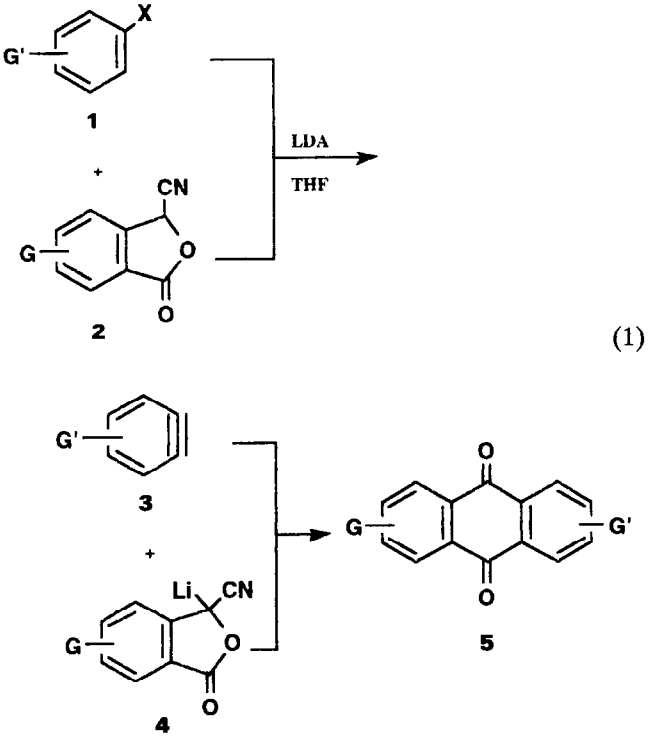
Abstract

Using 1,4-dipolar-aryne cycloaddition methodology, a convenient, short synthesis of several fluoroanthraquinones is presented which involves the reaction of haloarenes and 3-cyanophthalides in the presence of lithium diisopropylamide (LDA) in tetrahydrofuran (THF). The fluorine substituent(s) can be introduced by using fluorine-substituted haloarenes and/or 3-cyanophthalides. Similarly, fluorine-substituted pyridines can be prepared by treating fluorine-substituted cyanophthalides and halopyridines in the presence of lithium diisopropylamide.

Introduction

We recently reported short (usually one-step), efficient syntheses of tricyclic compounds such as anthraquinones [1, 2], aza-anthraquinones [3], anthracyclinones [2], 10-hydroxy-9-anthracenecarbonitriles [4], 10-amino-9-anthracenecarbonitriles [5] and aza-acridones [6]. The key step in this annulation methodology involves cycloadding 1,4-difunctional nucleophiles such as 3-lithio-3-cyanophthalides or α-cyano-α-lithio-*o*-toluonitrile to either arynes or hetarynes. Herein we report the extension of this [4+2] arynic methodology to the one-step synthesis of fluoroanthraquinones and fluoroaza-anthraquinones.

This methodology involves [eqn. (1)] generating an appropriately substituted aryne (**3a–d**) or hetaryne (**3e**) by the reaction of lithium diisopropylamide and the corresponding haloarene (**1a–d**) or halohetarene (**1e**) in the presence of a 3-lithio-3-cyanophthalide (**4a–d**). The lithiated species **4a–d** are prepared *in situ* by treating the corresponding 3-cyanophthalide (**2a–d**) with lithium diisopropylamide. The 3-cyanophthalide intermediate **4a–d** then cycloadds to the aryne (**3a–d**) or hetaryne (**3e–g**) to yield the corresponding anthraquinone (**5a–e**).



(1)

(X = Cl, Br; G, G' = substitution patterns)

This arynic method will permit the introduction of one or more fluorine substituents to the anthraquinone ring using either fluoro-substituted haloarenes and/or fluoro-substituted cyanophthalides. Since a large number of fluoro-substituted haloarenes are commercially available

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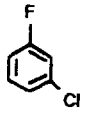
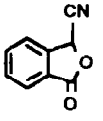
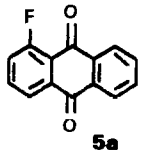
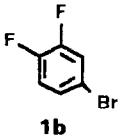
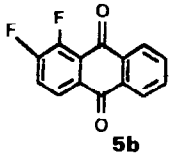
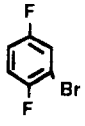
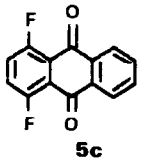
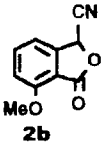
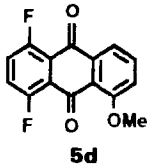
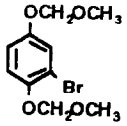
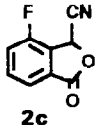
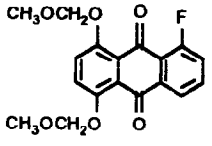
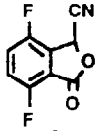
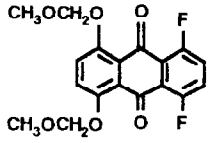
and fluoro-substituted cyanophthalides can be prepared conveniently from fluoro aromatic acids by the method of Swenton and coworkers [7], this method should provide ready access to fluoro derivatives of anthra- and aza-anthraquinones with a wide variety of substitution patterns.

Experimental

General procedure for the aryne reaction haloarenes and 3-cyanophthalides and LDA in THF

In a flame-dried flask flushed with nitrogen, lithium diisopropylamide (LDA) was prepared by adding n-butyllithium (30 mmol, 2.5 M in hexane) to a solution of diisopropylamine (30 mmol) in 40 ml of tetrahydrofuran (THF) at −78 °C under a nitrogen atmosphere (septum cap technique). After 10 min at −78 °C, the appropriate 3-cyanophthalide (10 mmol) in THF (40 ml) was added dropwise over 20 min and the reaction mixture stirred an additional 10 min at −78 °C. The mixture was then warmed to −40 °C, the haloarene added dropwise over a period of 10 min and the mixture allowed to warm to room temperature. The resulting dark reddish solution was quenched with methanol (2 ml), the THF evaporated (rotatory evaporator) and the residue extracted with CH_2Cl_2 (2 × 50 ml). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated (rotatory evaporator) to provide an oil, which was purified by flash column chromatography using a mixture of hexane/ethyl acetate (19:1 or 9:1, depending upon the polarity of the product) as eluent. The ^1H NMR spectra were recorded on an IBM/Bruker WP200SY NMR spectrometer using tetramethylsilane

TABLE 1. Anthraquinones (5a–f) prepared

Entry	Haloarene	Cyanophthalide	Anthraquinone	(yield, %)
1	 **1a**	 **2a**	 **5a**	(51)
2	 **1b**	**2a**	 **5b**	(45)
3	 **1c**	**2a**	 **5c**	(41)
4	**1c**	 **2b**	 **5d**	(51)
5	 **1d**	 **2c**	 **5e**	(47)
6	**1d**	 **2d**	 **5f**	(41)

as internal standard. The physical and ^{1}H NMR spectral properties of the compounds prepared are shown below.

1-Fluoroanthraquinone (**5a**): red solid, m.p. 197–199 °C. ^{1}H NMR ($CDCl_3$) δ: 7.53 (m, 2H); 7.82 (m, 2H); 8.1–8.17 (m, 1H); 8.23–8.28 (m, 2H) ppm. Analysis: Calc. for $C_{14}H_7FO_2$: C, 74.34; H, 3.12%. Found: C, 74.20; H, 3.18%.

1,2-Difluoroanthraquinone (**5b**): reddish-brown solid, m.p. 185–187 °C. ^{1}H NMR ($CDCl_3$) δ: 7.62–7.27 (m, 1H); 7.9–8.05 (m, 3H); 8.41–8.51 (m, 2H) ppm. Analysis: Calc. for $C_{14}H_6F_2O_2$: C, 65.70; H, 2.48%. Found: C, 65.81; H, 2.28%.

1,4-Difluoroanthraquinone (**5c**): orange solid, m.p. 205–207 °C. ^{1}H NMR ($CDCl_3$) δ: 7.51 (m, 2H); 7.77–7.82 (m, 2H); 8.21–8.3 (m, 2H) ppm. Analysis: Calc. for $C_{14}H_6F_2O_2$: C, 65.70; H, 2.48%. Found: C, 65.46; H, 2.38%.

5,8-Difluoro-1-methoxyanthraquinone (**5d**): orange solid. ^{1}H NMR ($CDCl_3$) δ: 4.02 (s, 3H); 6.91 (d, $J=7.5$ Hz, 1H); 7.02 (d, $J=7.5$ Hz, 1H); 7.35–7.86 (m, 3H) ppm. Analysis: Calc. for $C_{15}H_8F_2O_3$: C, 65.70; H, 2.74%. Found: C, 65.45; H, 2.58%.

5-Fluoro-1,4-bis(methoxy)methoxyanthraquinone (**5e**): dark orange solid, m.p. 140–141 °C. ^{1}H NMR ($CDCl_3$) δ: 3.67 (s, 3H); 3.68 (s, 3H); 5.29 (s, 2H); 5.31 (s, 2H); 7.43–7.67 (m, 4H); 7.80 (d, $J=7.5$ Hz, 1H) ppm. Analysis: Calc. for $C_{15}H_8F_2O_3$: C, 62.43; H, 4.37%. Found: C, 62.45; H, 4.53%.

5,8-Difluoro-1,4-bis(methoxy)methoxyanthraquinone (**5f**): dark orange solid. ^{1}H NMR ($CDCl_3$) δ: 3.54 (s, 6H); 5.28 (s, 4H); 7.36–7.41 (m, 4H) ppm. Analysis: Calc. for $C_{18}H_{14}F_2O_6$: C, 59.35; H, 3.87%. Found: C, 59.45; H, 3.74%.

5,8-Difluoro-2-aza-anthraquinone (**5g**): red solid, m.p. 194–195 °C. Analysis: Calc. for $C_{13}H_5F_2NO_2$: C, 63.68; H, 2.06; N, 5.71%. Found: C, 63.75; H, 2.04; N, 5.88%.

5-Fluoro-1,3-dimethoxy-2-aza-anthraquinone (**5h**): red solid, m.p. 234–236 °C. Analysis: Calc. for $C_{15}H_{10}FNO_4$: C, 52.87; H, 4.44; N, 6.17%. Found: C, 52.71; H, 4.37; N, 6.18%.

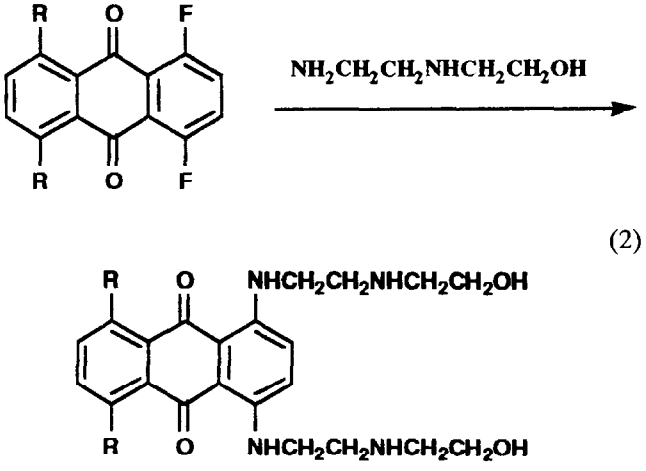
5,8-Difluoro-4-(methoxymethyl)methoxymethyl-2-aza-anthraquinone (**5i**): dark red solid, m.p. 194–195 °C. Analysis: Calc. for $C_{15}H_9F_2NO_4$: C, 59.02; H, 2.97; N, 4.59%. Found: C, 59.13; H, 3.07; N, 5.48%.

5,8-Difluoro-2-aza-anthraquinone (**5j**): dark red solid, m.p. 194–195 °C. Analysis: Calc. for $C_{13}H_5F_2NO_2$: C, 63.68; H, 2.06; N, 5.71%. Found: C, 63.43; H, 2.10; N, 5.92%.

5-Fluoro-1,3-dimethoxy-2-aza-anthraquinone (**5k**): Analysis: Calc. for $C_{15}H_{10}FNO_4$: C, 62.72; H, 3.51; N, 4.88%. Found: C, 62.43; H, 3.50; N, 5.02%.

Results and discussion

Our initial interest in extending the synthetic application of the aryne cycloaddition methodology for the preparation of fluorinated anthraquinones was to prepare 1-fluoro- and 1,4-anthraquinone analogs since these fluorine atoms can be easily replaced by nucleophiles. For example, mitoxantrone (**6a**) and ametantrone (**6b**), which show promise as potential clinical anti-tumor drugs [8], can be prepared [eqn. (2)] by treating the respective 1,4-difluoroanthraquinones (**5c** and **5l**) with 2-(2-aminoethylamino)ethanol [9].



(2)

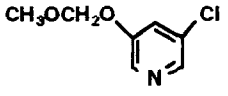
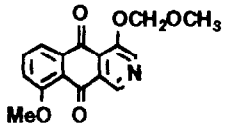
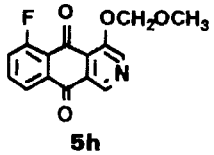
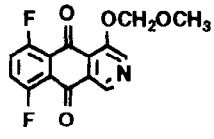
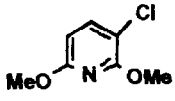
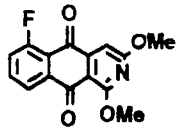
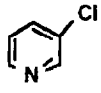
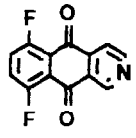
(**5l**) R = OH (**6a**) R = OH (mitoxantrone)
(**5c**) R = H (**6b**) R = H (ametantrone)

As shown in Table 1, 1,4-difluoroanthraquinone (**5c**), precursor to ametantrone (**2b**), was conveniently prepared (entry 3) from 2-bromo-1,4-difluorobenzene (**1c**) and 3-cyanophthalide (**2a**) in 41% yield. Additionally, treatment of 2-bromo-1,4-di(methoxymethylmethoxy)benzene (**1d**) and 4,7-difluoro-3-cyanophthalide (**2d**) gave 1,4-difluoro-5,8-dimethoxymethoxyanthraquinone (**5f**) in 41% yield (entry 6), which was easily converted to mitoxantrone in almost quantitative yield upon acidic hydrolysis.

The versatility of this arynic methodology is further shown by the regioselective cycloaddition of lithiated 3-cyanophthalides (**4a–d**) to arynes possessing strong *meta*-directing groups [10] such as fluoro (**3a**) generated from **1a**, difluoro (**3b**) generated from **1b** and methoxymethoxy (**3d**) generated from **1d**. For example, 1-fluoro (**5a**) (entry 1) and 1,2-difluoroanthraquinone (**5b**) (entry 2) were supplied in 51% and 45% yields, respectively, by the reaction of 3-cyanophthalide (**2a**) with 1-bromo-3-fluorobenzene (**1a**) and 1-bromo-3,4-difluorobenzene (**1b**) in the presence of lithium diisopropylamide.

As shown in Table 2, several 2-aza-anthraquinones (**5g–j**) were also prepared in fair to good yields (33%–71%) by the regioselective addition of 3-lithio

TABLE 2. Aza-anthraquinones (**5g–k**) prepared

Entry	Pyridyne	Cyanophthalide	Aza-anthraquinone	(yield, %)
1	 **1e**	**2b**	 **5g**	71
2	**1e**	**2c**	 **5h**	33
3	**1e**	**2d**	 **5i**	37
4	 **1f**	**2c**	 **5j**	51
5	 **1g**	**2d**	 **5k**	45

derivatives of the respective 3-cyanophthalide (**2b–d**) to 5-methoxymethoxy-3,4-pyridyne (**3e**) (entries 1–3) or 2,6-dimethoxy-3,4-pyridyne (**3f**) (entry 4). 3,4-Pyridyne (**3g**), unlike its aromatic analog benzyne, undergoes nucleophilic addition nonregioselectively, usually yielding inseparable isomeric mixtures. However, a single 2-aza-anthraquinone product can be obtained when **3g** is generated in the presence of 3-lithiated derivatives of 3-cyanophthalide or 4,7-disubstituted 3-cyanophthalides in which both substituents are identical. Thus, as shown in entry 5, Table 2, 5,8-difluoro-2-aza-anthraquinone (**5k**) was prepared in 45% yield by treating 3-chloropyridine (**1g**) with 3-cyano-4,7-difluorophthalide (**2d**). This convenient one-step synthesis of 2-aza-anthraquinones is especially noteworthy since aza-anthraquinones have been postulated to be effective DNA intercalates, and thus potential anti-tumor agents [11].

Acknowledgments

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References

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