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Convenient Syntheses of Substituted 7,12-Dioxa-benzo[*a*]anthracenes and 7,12-Dioxa-5-aza-benzo[*a*]anthracenes

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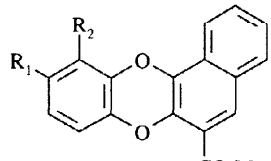
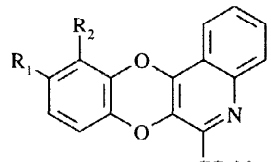
Abstract : The syntheses of 7,12-Dioxa-benzo[*a*]anthracenes bearing in C_6 a carboxymethyl group and 5-aza analogues are described. The key steps are intramolecular cyclisations of 3-arylbenzo[1,4]dioxin-2-diethylcarboxamides and palladium catalysed methoxycarbonylation of aryl triflates.

In the course of a research program directed toward the design of anticancer agents we prepared polycyclic heterocyclic derivatives exhibiting *in vitro* and *in vivo* antitumoral activity[1]. These compounds contain a planar benzodioxinic chromophore, with four or five fused rings, bearing a flexible amino-side chain.

With the intent of developing these promising series, we needed an easy procedure for the synthesis of benzodioxinic substructures **1** and **2** bearing a carboxymethyl group at C_6 :



1



2

a: $R_1 = H$, $R_2 = H$
b: $R_1 = H$, $R_2 = OMe$
c: $R_1 = OMe$, $R_1 = H$

We assumed that these derivatives could be obtained respectively from carboxamides **4** and **5** by cyclisation leading to a phenol **6** and a lactam **7**, and then formation and alkoxycarbonylation of the corresponding aryl triflates (Scheme 1).

We previously described[2] a general procedure for the preparation of 3-arylbenzo[1,4]dioxin-2-diethylcarboxamides *via* the palladium-catalysed cross-coupling of organotin reagents with aryl halides. This method was used to obtain the required derivatives **4** and **5** by coupling the appropriate stannanes **3** respectively with 2-iodotoluene and N-(*tert*-butoxycarbonyl)-2-iodoaniline.

The treatment of carboxamides **4** with lithium diisopropylamide (3eq.) at -78°C led to the desired tetracyclic derivatives **6** in good yields (Scheme 1).

Moreover, a simple acidic treatment of compounds **5** allowed the deprotection of the N-(*tert*-butoxycarbonyl) aniline moiety and a spontaneous cyclisation leading to the formation of lactam **7** (Scheme 1).

Palladium-catalysed alkoxycarbonylation involving triflates chemistry[3] was first realized on unsubstituted derivatives **6a** and **7a**.

The aryltriflate **8a** was obtained in 90% yield, at 0°C in dichloromethane by reaction of **6a** with trifluoromethanesulfonic anhydride (1.2 eq.) in the presence of pyridine (3 eq.)[3]. The treatment of lactam **7a**

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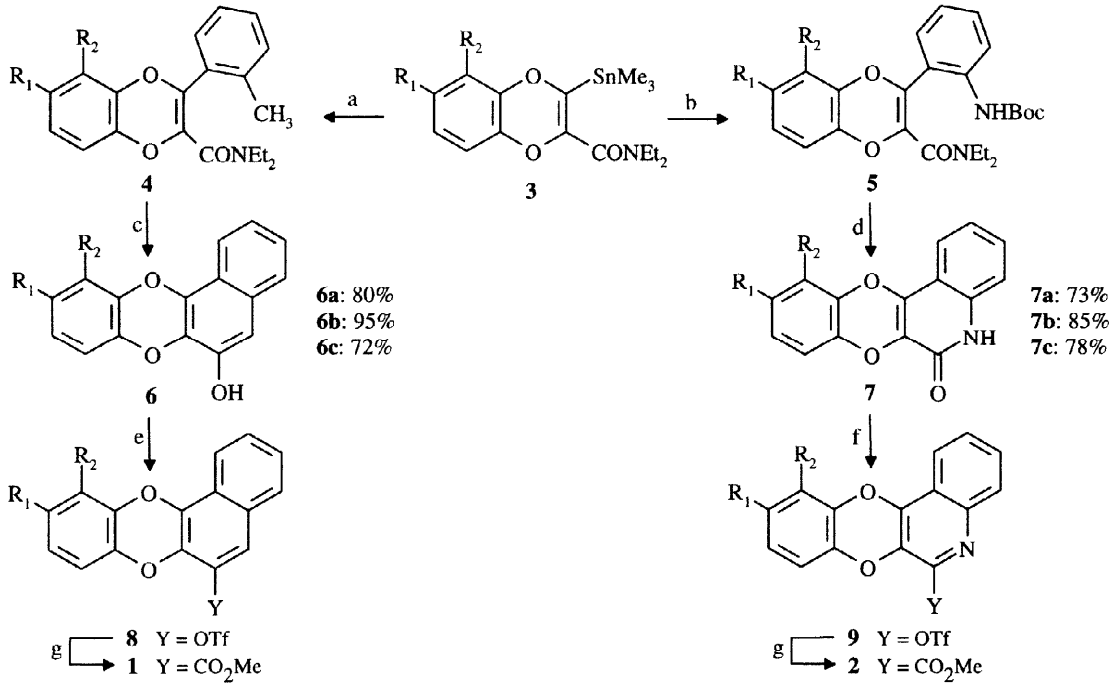
with sodium hydride (3 eq.) then N-phenyltrifluoromethanesulfonimide (2 eq.) in tetrahydrofuran and hexamethylphosphoramide afforded **9a** in 75% yield[4].

The conversion of **8a** and **9a** into the required methylesters **1a**[5] and **2a**[6] was finally achieved in both cases in 70% yield in dimethylsulfoxide, at 70°C under carbon monoxide ambient pressure employing $(dppp)Pd(OAc)_2$ as the catalyst (10%) in the presence of triethyamine (2 eq.) and methanol[7].

Scheme 1



a) 2-iodotoluene (1 eq.), $Pd(PPh_3)_4$ (10% mol), CuI (10% mol), 1,4 -Dioxane, reflux; b) N-(*tert*-butoxycarbonyl)-2 -iodoaniline (1 eq.), $Pd(PPh_3)_4$ (5% mol), CuI (5% mol), 1,4-Dioxane, reflux; c) LDA (3 eq.), THF, -78°C; d) HCl (6N), 1,4-Dioxane, 70°C; e) Tf_2O (2 eq.), Pyridine (3 eq.), CH_2Cl_2, 0°C; f) NaH (3 eq.), THF-HMPA, reflux, then $PhNTf_2$ (2 eq.); g) $(dppp)Pd(OAc)_2$ (10% mol), NEt_3 (2 eq.), MeOH, DMSO, CO, 70°C.

We have developed a versatile method for the preparation of new heterocyclic systems to be used in the elaboration of antitumoral compounds.

References and notes

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2. Khatib, S.; Mamai, A.; Guillaumet, G.; Bouzoubaa, M.; Coudert, G. *Tetrahedron Lett.*, **1997**, *38*, 5635-5638.
3. Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis*, **1982**, 85-126.
4. Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc. Chem. Commun*, **1987**, 904-905.
5. Data for compound **1a**: m. p. 122-124°C; IR (KBr): 1700 cm^{-1} (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 3.93 (s, 3H, CO_2Me), 6.99 (m, 4H, H-8 ,H-9 ,H-10, H-11), 7.41 (m, 1H, H-3), 7.54 (m, 1H, H-2), 7.75 (m, 1H, H-4), 8.02 (s, 1H, H-5), 8.04 (m, 1H, H-1); ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 52.4, 116.3, 116.9, 119.4, 120.4, 124.3, 124.4 , 125.7, 125.8, 126.6, 128.4, 128.6, 128.9, 130.9, 136.4, 136.7, 142.2, 165.4; MS (CI/NH_3): m/z (%) 293 (MH^+).
6. Data for compound **2a**: m. p. 132-134°C; IR (KBr): 1738 cm^{-1} (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 4.07 (s, 3H, CO_2Me), 6.95-7.05 (m, 4H, H-8, H-9, H-10, H-11), 7.53-7.70 (m, 2H, H-2, H-3), 7.99-8.10 (m, 2H, H-1, H-4); ^{13}C NMR (62.89 MHz, $CDCl_3$): δ 53.1, 116.8, 117.3, 120.2, 120.4, 124.5, 124.8, 125.4, 125.6, 128.4, 129.4, 129.9, 134.1, 141.5, 144.6, 146.2, 164.3; MS (IS): m/z (%) 294 (MH^+).
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