THE REGIOSPECIFIC SYNTHESIS OF ORTHO AMINONAPHTHOPHENONES VIA THE ADDITION OF CARBANIONS TO NAPHTHOXAZIN-4-ONES

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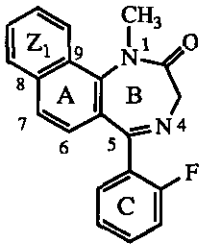
Abstract- The conversion of nitronaphthalenes(see **4a** and **4b**) into the corresponding ortho aminonaphthylnitriles(**5a** and **5b**) via the process of Tomioka, when combined with the addition of carbanions to the intermediate naphthoxazin-4-ones, provided a route to ortho aminonaphthophenones (**7a**) and (**7b**). These key intermediates were employed to synthesize the benzfused 2'-fluoro-1,4-benzodiazepines (**1-3**).

Alpha aminobenzophenones have been widely employed for the synthesis of heterocyclic compounds including the 1,4-benzodiazepines.[1-4] Recently the need arose for a preparation of the benzfused benzodiazepine analogs (**1**, **2** and **3**) in order to probe the spatial dimensions of benzodiazepine receptor binding sites.[5] These "molecular yardsticks" with the rigid benzfused ring(Z_1, Z_2 and Z_3) are being employed to determine the size of lipophilic pockets L_2 and L_3 in the benzodiazepine receptor cleft,[5] as well as the effect of occupation of these pockets on anxiolytic activity.[6]



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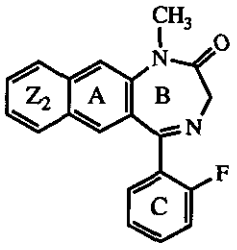

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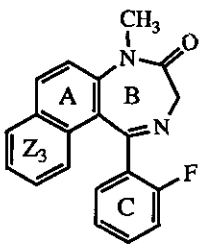

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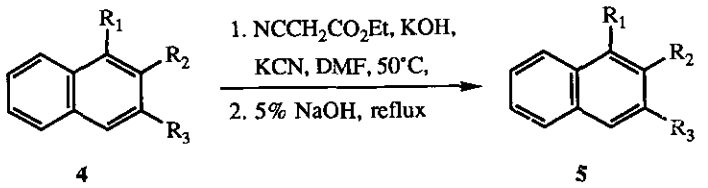
Although α-aminobenzophenones have been employed earlier as key intermediates for the preparation of 1,4-benzodiazepines,[1-4] extension to a naphthyl ring system had not been reported. In 1980 Tomioka et al.[7] developed a novel one pot sequence in which substituted nitrobenzenes could be converted into ortho-aminobenzonitriles. In this manner 1-nitronaphthalene (**4a**) and 2-nitronaphthalene (**4b**) were heated individually to 50°C in the presence of ethyl cyanoacetate, potassium cyanide and potassium hydroxide for 36 hours. This was followed by hydrolysis,[8] as depicted in Scheme I, to furnish 1-amino-2-naphthylnitrile (**5a**) and 2-amino-1-naphthylnitrile (**5b**), respectively. Regiospecific orthocyanation of the nitronaphthyl derivative with concomitant reduction of the nitro moiety to an amino function had occurred in the same simple sequence.

The aminonaphthylnitiles (**5a**) and (**5b**) were stirred with three equivalents of phenyl magnesium bromide, under Barbier-Grignard conditions, in refluxing ether and this process was followed by hydrolysis, to provide the 1-amino-2-benzoyl-naphthalene (**6a**) and 2-amino-1-benzoylnaphthalene (**6b**) in greater than 85% yield (Scheme I). For the synthesis of 2-amino-3-benzoylnaphthalene (**6c**), 3-amino-2-naphthoic acid (**5c**) was stirred with three equivalents of phenyllithium in refluxing THF to furnish **6c** in 51% yield, accompanied by 10% of the related carbinol. Although **6a-6c** could be transformed into the parent(2'-H) systems

Scheme I

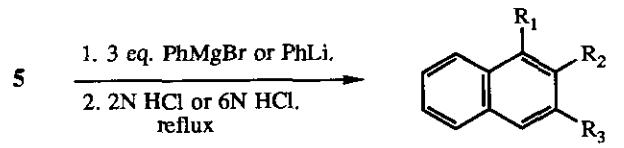


4

a. R_1=NO_2, R_2=H, R_3=H
b. R_1=H, R_2=NO_2, R_3=H

5

a. R_1=NH_2, R_2=CN, R_3=H
b. R_1=CN, R_2=NH_2, R_3=H
c. R_1=H, R_2=CO_2H, R_3=NH_2
d. R_1=NH_2, R_2=CO_2H, R_3=H



6

a. R_1=NH_2, R_2=COPh, R_3=H
b. R_1=COPh, R_2=NH_2, R_3=H
c. R_1=H, R_2=COPh, R_3=NH_2

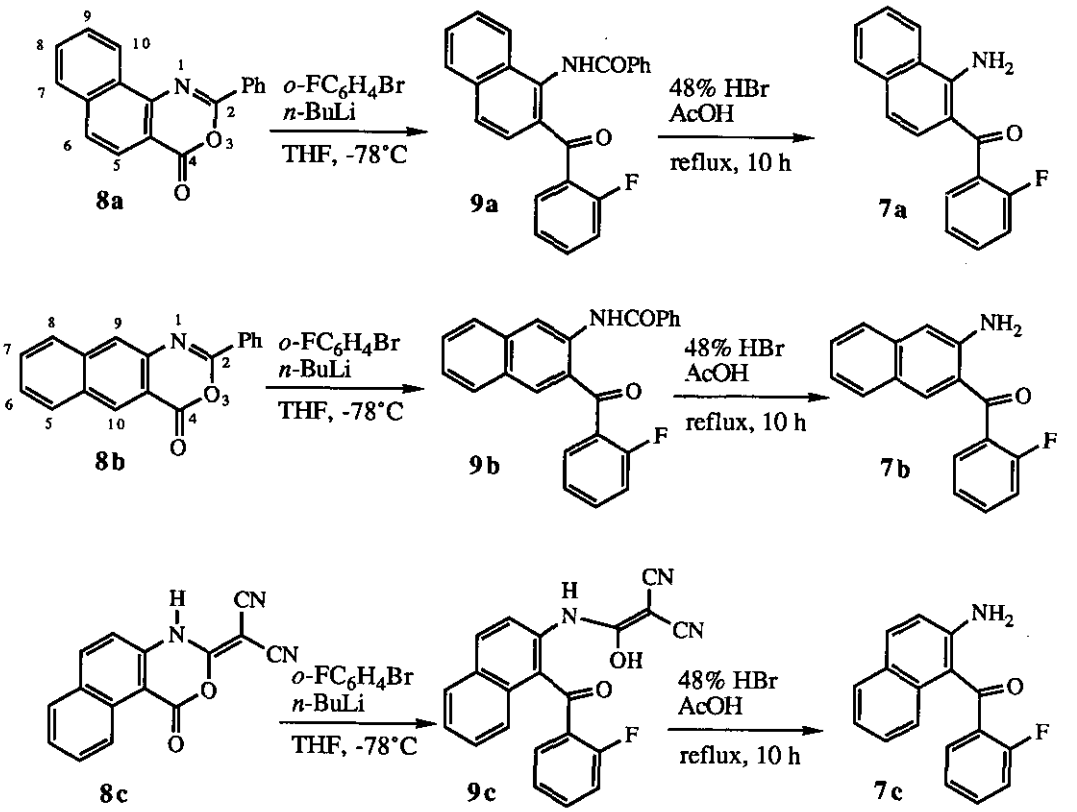
related to **1-3** via published methods,[1-4] efforts to convert **5a-5c** into the desired 2'-fluoro congeners (**7a-7c**) on stirring with 2-fluorobromobenzene/n-butyllithium (-50°C to -78°C) failed. At low temperature the 2-fluorophenyllithium would not react with the electrophilic center in **5a-5c**; moreover, at temperatures above -30°C elimination of fluorine occurred to provide biphenylene, presumably via a benzyne intermediate.

Clemence et al.[9] had demonstrated, however, that benzoxazin-4-ones react with dianions at low temperature (-70°C) while Hromatka had converted thieno[1,3]oxazin-4-ones into α-aminothiophenones under similar conditions.[10] For these reasons orthoaminonitrile (**5a**) was hydrolyzed (20% NaOH, ethanol, 78°C) to provide the corresponding 1-amino-2-naphthoic acid (**5d**) but attempts to execute

the analogus conversion with **5b** failed to yield the corresponding 2-amino-1-naphthoic acid due to the predisposition of this amino acid toward decarboxylation.[11]

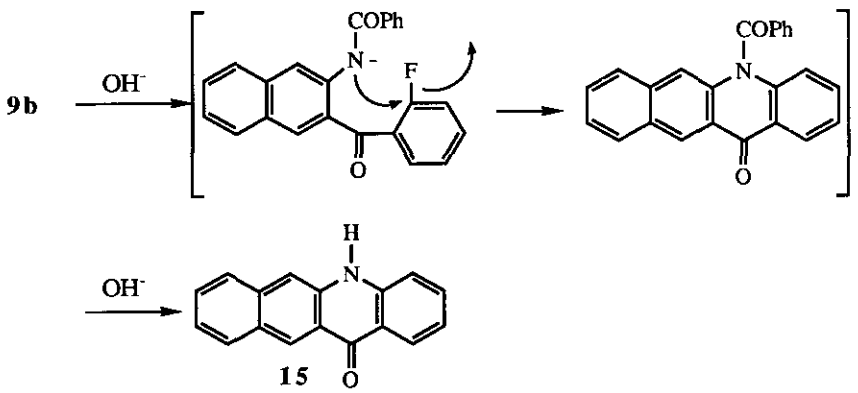
The two aminonaphthoic acids (**5d**) and (**5c**) were heated in excess benzoyl chloride[9] at 130°C to furnish the 2-phenyl-4H-naphtho[1,2-d]-1,3-oxazin-4-one (**8a**) and 2-phenyl-4H-naphtho[2,3-d]-1,3-oxazin-4-one (**8b**), respectively. Treatment of **8a** and **8b** with one equivalent of 2-fluorophenyllithium at -78°C, followed by hydrolysis under acidic conditions gave the desired 1-amino-2-

Scheme II



(2'-fluorobenzoyl)naphthalene (**7a**) and 2-amino-1-(2'-fluorobenzoyl)naphthalene (**7b**)[12] in 90% and 54% yields, respectively. Since the starting amino acid for preparation of **7c** was not readily available,[11] a related intermediate (**8c**) from the Tomioka[13] process was prepared and converted into 2-amino-3-(2'-fluorobenzoyl)naphthalene (**7c**) via **9c**, in 70% yield, as illustrated in Scheme II. The hydrolysis of amide (**9b**) under basic conditions gave the acridine derivative (**15**) quantitatively, as shown in Scheme III. This reaction may provide a mild and efficient synthesis of benzfused acridines. The three fluoroaminonaphthylketones (**7a-7c**) depicted in Scheme II were transformed into the corresponding 2'-fluorobenzfused benzodiazepines (**1-3**) under the standard conditions of Sternbach[2] and Fryer.[14]

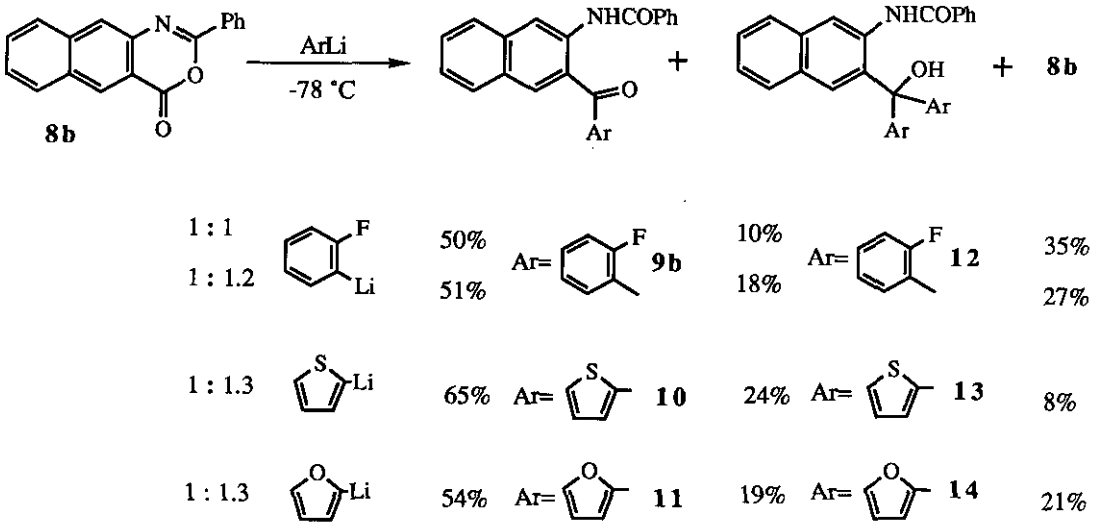
Scheme III



It was earlier reported[9,15] that the reaction of carbanions with 1,3-benzoxazin-4-ones took place in yields of 20-40%; however, in the present cases the yields varried from 50-90%. The addition of carbanions to the naphthoxazin-4-ones at low temperature to provide the corresponding amino ketones (Scheme IV) appears to be general. Addition of 2-fluorophenyllithium, 2-thienyllithium or 2-furyllithium at -78°C to naphthoxazine (**8b**) provided reasonable yields of the arylketones (**9b**,

10, and 11), respectively. The advantage of the aryloxazine intermediates (e.g. see **8b**, Scheme III) arises from the ability to employ low temperatures in the process compatible with the lability of the aryllithium reagents. In addition, the facile conversion of **4a** and **4b** into the corresponding α-aminonaphthylnitrile intermediates (**5a**) and (**5b**) extends the scope of the novel transformation introduced by Tomioka et al.[8]

Scheme IV



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12. **7a:** mp 119-120 °C; ^{1}H nmr($CDCl_3$) δ 7.96 (d, 1H, *J*=8.4 Hz), 7.71 (dd, 1H, *J*=1.2, 8.3 Hz), 7.70 (br s, 2H, NH_2), 7.57 (dt, 1H, *J*=1.2, 8.1 Hz), 7.51-7.41 (m,, 3H), 7.30-7.11 (m, 3H), 6.94 (d, 1H, *J*=8.3 Hz); ir(KBr): 3499, 3377(NH_2), 1612(C=O)(cm^{-1}); ms(EI): m/z 265(91), 264(87), 246(30) 115(100). **7b:** mp 107.9-109.0 °C; ^{1}H nmr(DMSO-d_6) δ 8.17 (d, 1H, *J*=2 Hz), 7.82-7.72 (m, 4H), 7.65 (dt, 1H, *J*=1, 6.6 Hz), 7.52 (dt, 1H, *J*=1, 6.6 Hz), 7.48-7.35 (m, 3H), 7.24 (s, 1H), 6.12 (br s, 2H, NH_2); ir(KBr): 3483, 3372(NH_2), 1628, 1605(cm^{-1}); ms(EI): m/z 265 (83), 264 (52), 115(100). **7c:** mp 98.1-99.3 °C; ^{1}H nmr($CDCl_3$): δ 7.72 (d, 1H, *J*=9 Hz), 7.62 (dd, 1H, *J*=1.5, 9 Hz), 7.17-7.40 (m, 2H), 7.26 (d, 1H, *J*=9 Hz), 7.17-6.98 (m, 4H), 6.90 (d, 1H, J=9 Hz), 5.60 (br s, 2H, NH_2); ir(KBr): 3494, 3381(NH_2), 1645, 1620, 1602(C=O), (cm^{-1}); ms(EI):m/z 265(100), 264(71), 170(75), 115(90).

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