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Direct regioselective phenylation of acridine derivatives by phenyllithium

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Abstract—Acridine and acridine derivatives have been converted directly to phenyl derivatives regioselectively using phenyllithium.

Alkylation of acridine and acridine derivatives improves their solubility in common organic solvents.[1] Direct phenylation of acridine and its derivatives using phenyllithium would generate phenylacridines which are building blocks/motifs of various polycyclic natural and unnatural products.[1,2] Michael type 1,4-addition of phenyllithium to the pyridine nucleus leads to the only product isolated from the reaction mixture. Direct phenylation will further help to prepare functionalised aryl moieties which could be cyclised to generate aza-congeners of polycyclic aromatic hydrocarbons (PAH). As a part of our program on the synthesis of bioactive acridines, we present here a general method for phenylation directed by the nitrogen of acridine derivatives at specific sites. We are interested in applying the novel phenylation protocol to the *C*-arylation of benz- and dibenzacridines.

When acridine **1** was treated with phenyllithium–TMEDA, 0°C in THF, followed by quenching the reaction mixture with water, 9-phenyl-9,10-dihydroacridine **8a** was generated in 85% yield (Table 1, entry 1). This compound upon treatment with DDQ in refluxing benzene produced 9-phenylacridine[3] in 90% yield. On changing the quenching agent from H_2O to D_2O, incorporation of deuterium was observed on the nitrogen leading to compound **8b** in 82% yield (Table 1, entry 2). Under identical conditions changing the quenching agent from D_2O to CH_3I or C_2H_5Br generated 10-methyl-9-phenyl-9,10-dihydroacridine or 10-ethyl-9-phenyl-9,10-dihydroacridine in 80 and 48% yields, respectively (Table 1, entries 3 and 4).

Similarly, benz[*c*]acridine[4] **2** upon treatment with phenyllithium–TMEDA at 0°C followed by quenching the reaction mixture with water produced 7-phenyl-7,12-dihydrobenz[*c*]acridine **9a** in 75% yield (Table 1, entry 5). Incorporation of deuterium on the nitrogen was observed, the product **9b** being isolated in 67% yield (Table 1, entry 6) when the reaction mixture was quenched with D_2O instead of water. Changing the quenching agent to CH_3I or C_2H_5Br led to the incorporation of a methyl or ethyl group onto the nitrogen (Table 1, entries 7 and 8). However with isopropyl bromide, *N*-alkylation was not observed. This may be due to the bulkiness of the isopropyl group. In the presence of a chiral diamine such as (−)-sparteine, the reaction product from acridine derivatives with phenyllithium showed optical activity, e.g. compound **10e** after reaction with phenyllithium in the presence of (−)-sparteine[5] in THF showed a specific rotation of +29 ($CHCl_3$, *c* 0.008); (e.e. 20%).

The effect of ring substituents on this reaction was studied and in many cases 1,4-addition of PhLi was observed. Thus, dibenz[*c*,*h*]acridine[6,7] **3a**, and 3-methoxy dibenz[*c*,*h*]acridine **3b**, when treated with PhLi followed by quenching with H_2O (Table 1, entries 9 and 10), D_2O (Table 1, entries 11 and 12), CH_3I (Table 1, entries 13 and 14) and C_2H_5Br (Table 1, entries 15 and 16) produced **10a**, **10e**, **10b**, **10f**, **10c**, **10g** and **10d**, **10h**, respectively.

An interesting observation was noticed in the case of dibenz[*c*,*f*]acridine **4**, (Table 1, entry 17) where no phenylation was observed. This may be due to the bulkiness of the phenyl group, which inhibits the reaction. In contrast, acenaphthoquinolines i.e., acenaph-

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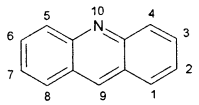

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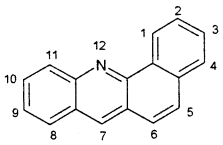

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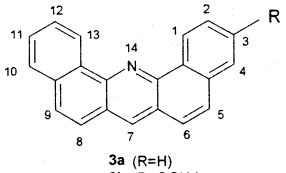
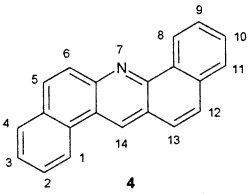


3a (R=H)
3b (R=OCH_3)



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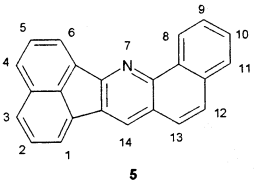

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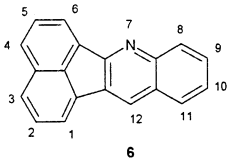

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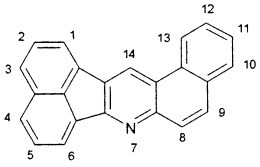

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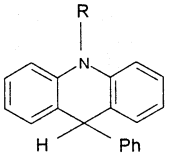
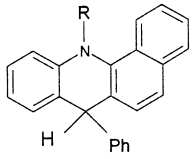
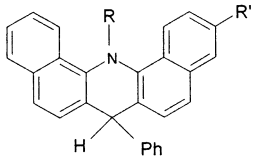


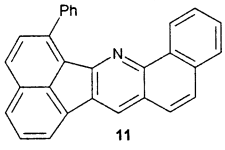
8a (R=H), **8c** (R=CH_3)
8b (R=D), **8d** (R=C_2H_5)



9a (R=H), **9c** (R=CH_3)
9b (R=D), **9d** (R=C_2H_5)



10a (R=H, R'=H),
10b (R=D, R'=H),
10c (R=CH_3, R'=H),
10d (R=C_2H_5, R'=H),
10e (R=H, R'=OCH_3)
10f (R=D, R'=OCH_3)
10g (R=CH3, R'=OCH_3)
10h (R=C_2H_5, R'=OCH_3)



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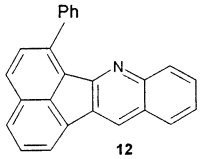

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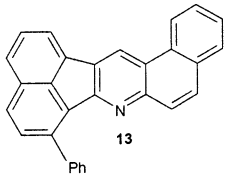

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tho[1,2-*b*]benzo[*f*]quinoline **5**, acenaphtho[1,2-*b*]-quinoline **6** and acenaphtho[1,2-*b*]benzo[*h*]quinoline[8] **7** were phenylated, and oxidised presumably by aerial oxidation during acidic workup, exclusively in the semi-bay region of the acenaphthene moiety, which again was influenced by the position of the heteroatom. This was indicated by the disappearance of the doublet at δ 8.40–8.51 and retention of the singlet at δ 8.48–9.29 in the ^{1}H NMR spectrum, which demonstrated that in compounds **5**, **6** and **7** the 6 position is phenylated exclusively. Although there are two positions available for Michael type addition, exclusive phenylation at C-6 is due to the 'proximity effect'. This was further proved by single-crystal X-ray analysis of butylated acenaphthoquinolines.[9]

In conclusion, this method is a simple one-pot, one-step technique for preparing a wide variety of phenylacridines and *N*-substituted acridines. Increasing the reaction time did not improve the yield. The *N*-methyldihydroacridine derivatives can also act as catalysts in photo radical cyclisation reactions.[10]

Table 1.

Entry	Compound	Reagents and conditions	Product[a]	Yield (%)
1	**1**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) H_2O	**8a**	85
2	**1**	(i) PhLi–THF–TMEDA/0°C, 1.5 h; (ii) D_2O	**8b**	82
3	**1**	(i) PhLi–THF–TMEDA/0°C, 4 h; (ii) CH_3I	**8c**	80
4	**1**	(i) PhLi–THF–TMEDA/0°C, 4 h; (ii) C_2H_5Br	**8d**	48
5	**2**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) H_2O	**9a**	75
6	**2**	(i) PhLi–THF–TMEDA/0°C, 1.5 h; (ii) D_2O	**9b**	67
7	**2**	(i) PhLi–THF–TMEDA/0°C, 4 h; (ii) CH_3I	**9c**	52
8	**2**	(i) PhLi–THF–TMEDA/0°C, 4 h; (ii) C_2H_5Br	**9d**	42
9	**3a**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) H_2O	**10a**	71
10	**3b**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) H_2O	**10e**	70
11	**3a**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) D_2O	**10b**	51
12	**3b**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) D_2O	**10f**	63
13	**3a**	(i) PhLi–THF–TMEDA/0°C, 4 h; (ii) CH_3I	**10c**	55
14	**3b**	(i) PhLi–THF–TMEDA/0°C, 5 h; (ii) CH_3I	**10g**	60
15	**3a**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) C_2H_5Br	**10d**	58
16	**3b**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) C_2H_5Br	**10h**	45
17	**4**	(i) PhLi–THF–TMEDA/0°C, 2 h; (ii) H_2O	No reaction	–
18	**5**	(i) PhLi–THF–TMEDA/0°C, 4 h; (ii) H_2O	**11**	69
19	**6**	(i) PhLi–THF–TMEDA/0°C, 5 h; (ii) H_2O	**12**	78
20	**7**	(i) PhLi–THF–TMEDA/0°C, 4 h; (ii) H_2O	**13**	77

[a] Products were identified from analytical and spectroscopic data.

Typical experimental procedure: To an ice-cold solution of the acridine (0.22 mmol) in dry THF (5–10 mL) and TMEDA (0.5–0.8 mL) under an argon atmosphere, 3–4 equiv. of PhLi solution in diethyl ether was added dropwise. After stirring at 0°C for 0.5 h the reaction mixture was quenched with the appropriate electrophile. Stirring was continued until the completion of the reaction. The reaction mixture was poured into ice-cold water and extracted with $CHCl_3$. The organic layer was washed with dil. HCl and water and the solvent was dried over anhydrous Na_2SO_4. Removal of the solvent furnished the crude product, which was purified by column chromatography (neutral alumina/*n*-hexane–ethyl acetate).

Selected spectroscopic data for compound 8d:
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.41 (t, 3H, $J=7.0$ Hz), 4.04 (q, 2H, $J=7.0$ Hz), 5.22 (s, 1H), 6.89 (dt, 2H, $J=7.31$, 0.91 Hz), 7.01–7.25 (m, 11H, aromatic H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 11.54, 40.05, 48.30, 112.51, 120.38, 125.20, 126.20, 127.29, 127.46, 128.45, 129.32, 140.49, 146.43.

Anal. calcd for $C_{21}H_{19}N$: C, 88.42; H, 6.66; N, 4.91. Found: C, 88.25; H, 6.52; N, 4.85.

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