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Highly site-selective alkylation reaction of bent aza-heterocycles by alkyllithium and alkyl halides

Dipanjan Pan, Bidhan C. Roy, Gandhi K. Kar and Jayanta K. Ray *

Department of Chemistry, Indian Institute of Technology, Kharagpur-721302, India

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Cavity-shaped azaarenes have been converted to site-selective alkyl derivatives by alkyllithium and alkyl halides.

Recently, it has been shown that alkylated acridine derivatives are good building blocks and receptors for molecular vernier and other novel molecular architectures.[1,2] Alkylation improves the solubility of the acridine derivatives in common organic solvents.[2] On the other hand regioselective alkylation of poly-aromatic compounds in the bay region can help chemists to achieve direct entry to alkylated acridines, which are bioactive systems.[3] As part of a programme on the synthesis of bioactive alkylated acridines, we present here a general method for alkylation, directed by the nitrogen atom of bent azaarenes at specific sites. We also decided to study the prospect of applying the novel alkylation protocol to the *C*-alkylation of benz- and dibenzacridines.

Thus, benz[*c*]acridine[4] (**1**) on treatment with *n*-BuLi–TMEDA, 0 °C followed by quenching of the reaction mixture with water generated 7-*n*-butyl-7,12-dihydrobenz[*c*]acridine (**11a**) in 60% yield (Table 1 entry no. 1). Thus the *n*-butyl group was introduced through 1,4-addition to the pyridine nucleus of the acridine moiety. In the presence of excess *n*-BuLi, selective deprotonation also takes place, generating aryllithiation in the bay region, which is supported by the following observation. When compound **1** was treated with an excess of *n*-BuLi and then quenched with D_2O (instead of water) incorporation of deuterium was observed on both N and C-1 to form compound **11b** (Table 1 entry no. 2) in 79% yield.

Under identical conditions, reaction of benz[*c*]acridine with *n*-BuLi at 0 °C followed by quenching the reaction mixture with MeI, produced 1,12-dimethyl-7-*n*-butyl-7,12-dihydrobenz[*c*]-acridine (**11c**) in 72% yield (Table 1 entry no. 3). This proves that the lithiation by *n*-BuLi at N and C-1 is pronounced presumably owing to the complex induced proximity effect

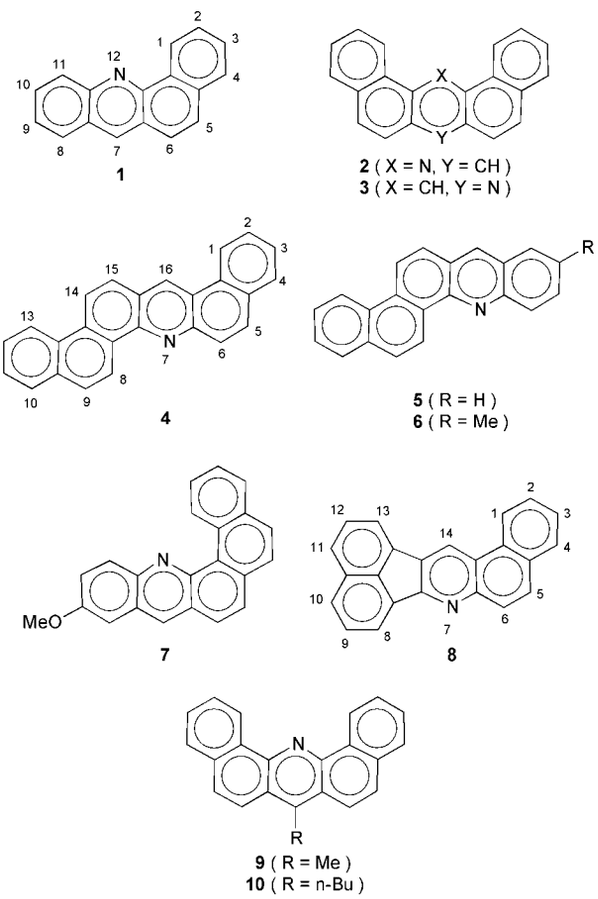

Table 1 Reaction of azaarenes with suitable alkyllithiums and alkyl halides

Entry no.	Compound (no.)	Reagent and conditions	Product[a] yield (%)
1	**1**	i) *n*-BuLi–THF–TMEDA/0 °C, 1.5–2 h; ii) H_2O	**11a** (60%)
2	**1**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) D_2O	**11b** (79%)
3	**1**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**11c** (72%)
4	**1**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) EtBr	**11d** + **11e** (69%) (1:4)
5	**2**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) D_2O	**12a** (89%)
6	**2**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**12b** (74%)
7	**5**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**13** (63%)
8	**6**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**14** (70%)
9	**4**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**15a** (68%)
10	**4**	i) MeLi–THF–TMEDA/0 °C, 1/2 h; ii) H_2O	**15b** (59%)
11	**7**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**16** (61%)
12	**3**	i) *s*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**17** (77%)
13	**1**	i) *t*-BuLi–THF–TMEDA/0 °C, 1.5–2 h; ii) H_2O	**11f** (51%)
14	**2**	i) *t*-BuLi–THF–TMEDA/0 °C, 1.5–2 h; ii) H_2O	**12c** (49%)
15	**4**	i) *t*-BuLi–THF–TMEDA/0 °C, 1.5–2 h; ii) H_2O	**15c** (48%)
16	**8**	i) *t*-BuLi–THF–TMEDA/0 °C, 1.5–2 h; ii) H_2O	**18** (54%)
17	**10**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**12d** (90%)
18	**9**	i) *n*-BuLi–THF–TMEDA/0 °C, 1/2 h; ii) MeI	**12e** (59%)

[a] All the products gave satisfactory NMR and microanalysis data.

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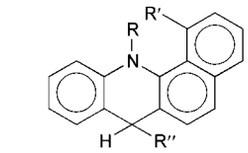
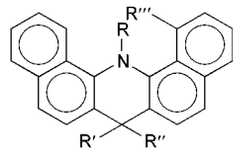
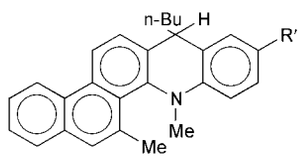


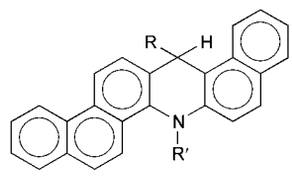
11a (R = R′ = H, R″ = n-Bu)
11b (R = R′ = D, R″ = n-Bu)
11c (R = R′ = Me, R″ = n-Bu)
11d (R = R′ = Et, R″ = n-Bu)
11e (R = Et = R′ = H, R″ = n-Bu)
11f (R = R′ = H, R″ = t-Bu)



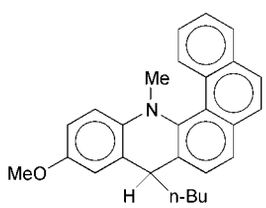
12a (R = R‴ = D, R″ = n-Bu, R′ = H)
12b (R = R‴ = Me, R″ = n-Bu, R′ = H)
12c (R′ = R‴ = R = H, R″ = t-Bu)
12d (R′ = R″ = n-Bu, R = R‴ = Me)
12e (R = R′ = R‴ = Me, R″ = n-Bu)



13 (R′ = H)
14 (R′ = Me)



15a (R = n-Bu, R′ = Me)
15b (R = Me, R′ = H)
15c (R = t-Bu, R′ = H)



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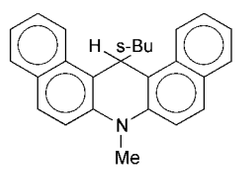

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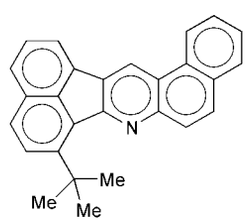

18

(CIPE).[5] Changing the quenching agent to other electrophiles, for example, EtBr produced a mixture of **11d** and **11e** (in 1 : 4 ratio) in overall 69% yield (Table 1 entry no. 4). However with isopropyl bromide neither *N*-alkylation nor *C*-alkylation was observed and the only product isolated was **11a**. This was probably due to steric reasons.

The effect of ring substituents on this reaction was then studied and in many cases bay region lithiation along with 1,4-addition of RLi were observed. Thus dibenz[*c*,*h*]acridine (**2**)[6,7] when treated with *n*-BuLi and then quenched with either D_2O (Table 1 entry no. 5) or with MeI (Table 1 entry no. 6) produced **12a** or **12b**, respectively as the only isolable products and this demonstrates the 1,4-addition reaction of *n*-BuLi as well as monolithiation in the bay region of the molecule. When naphtho[2,1-*c*]acridine derivatives **5** and **6** were allowed to react with *n*-BuLi at 0 °C followed by treatment with MeI, **13** (Table 1 entry no. 7) and **14** (Table 1 entry no. 8) respectively were produced in high yield. Interestingly in this system, out of the three bay region carbons (C-6, C-11 and C-12) lithiation was directed by N and was selective on C-6 only.

However an exception was observed with benzo[*a*]naphtho-[2,1-*h*]acridine (**4**) in these reactions. Compound **4** on reaction with RLi produced only the 1,4-addition product (to the pyridine nucleus) to give **15a** (when R = *n*-Bu and quenched with MeI) (Table 1 entry no. 9) or **15b** (when R = Me and quenched with water) (Table 1 entry no. 10) respectively. No methylation at the ring carbons was observed in the former case and indicates that lithiation at the bay region did not happen at all. The reason for such behaviour is unknown. In addition, naphthoacridine derivative **7** (having an N in a fjord region) showed no aryllithiation but preferential 1,4-addition was observed, and compound **16** was produced with *n*-BuLi and MeI (Table 1 entry no. 11). Dibenz[*a*,*j*]acridine (**3**) also reacted in a similar fashion with *s*-BuLi and MeI to furnish **17** (Table 1 entry no. 12). Thus alkyllithium and alkyl halides can be used as site selective alkylating agents in general (with some exceptions) for benzacridine derivatives. To the best of our knowledge such highly regioselective alkylation reactions of benz[*c*]acridine derivatives have not been reported before. Interestingly *t*-BuLi can also be used instead of other alkyllithium reagents for alkylation of different polycyclic azaarenes (PAA). Thus benz[c]acridine (**1**) on reaction with *t*-BuLi–TMEDA–THF, 0 °C and then quenching with water generated 7-*tert*-butyl-7,12-dihydrobenz[*c*]acridine (**11f**) in 74% yield (Table 1 entry no. 13).

Analogous 1,4-additions between benzacridine derivatives and *t*-BuLi were observed for compounds **2** and **4** and produced **12c** (Table 1 entry no. 14) and **15c** (Table 1 entry no. 15) respectively. However with acenaphtho[1,2-*b*]benzo[*f*]quinoline (**8**), the *t*-Bu group was introduced at the semi bay region carbon (C-8) close to the heteroatom to form exclusively compound **18** in 54% yield (Table 1 entry no. 16). Thus bulkier alkyl groups like the *t*-Bu group can also be introduced in the PAA moiety by this novel peri alkylation strategy. When dibenz[*c*,*h*]acridine (**2**) was treated with i) *n*-BuLi ii) H_2O only 7-*n*-butyl-7,12-dihydrodibenz[*c*,*h*]acridine was observed; use of excess butyllithium did not provide further butylation. Interestingly, when this dihydroderivative was dehydrogenated to **10** (with DDQ–benzene) and further treated with *n*-BuLi, it produced a *gem* dibutylated intermediate which on quenching with MeI generated exclusively **12d** (in excellent yield) in which both the C-1 and N atoms have methyl groups attached (Table 1 entry no. 17). Similar results were obtained when compound **9** was subjected to the same alkylation reaction with *n*-BuLi and MeI and the product formed in this case was **12e** (Table 1 entry no. 18).

This one-pot one-step technique for the synthesis of a wide variety of alkylated azaarenes not only regioselectively introduces alkyl groups at appropriate positions but also allows further functionalisation to be easily achieved. In addition the *N*-methyldihydroacridine derivatives can also act as catalysts in photoradical cyclisation reactions.[8] A further bonus of this study is the generation of a tetrahedral carbon (*e.g.*, C-7 of **11** and **12e**, C-9 of **16**, C-14 of **13** or **14** and C-16 of **15**), which could be made chiral, by carrying out the reaction with RLi in the presence of a chiral diamine like (−)-sparteine, and the substrates could be used as chiral receptors. Application of this strategy is in progress in our laboratory.

In conclusion this type of alkylation reaction is highly regioselective and sensitive to the nature of substrate and reaction conditions. The optimum conditions for alkylation at the bay region of appropriate systems are given in the general experimental procedure. A longer reaction time resulted in no increase in the product yield.

General experimental procedure

To an ice cooled solution of azaarene in THF and TMEDA (0.3–0.5 ml), RLi (3–4 equiv.) was added dropwise. It was stirred at 0 °C for 0.5 h and quenched with the appropriate electrophile. After stirring for an additional 0.5 h, the reaction mixture was poured into crushed ice and extracted with $CHCl_3$. It was washed with water several times and dried over Na_2SO_4. Removal of solvent afforded the desired product in high yield (see Table 1).

Selected data for 11a

δ_H ($CDCl_3$, 300 MHz): 0.79 (t, 3H, *J* 6.6 Hz), 1.18–1.25 (m, 4H), 1.64–1.66 (m, 2H), 4.10 (t, 1H, *J* 6.3 Hz), 6.73 (br s, 1H), 6.87–6.97 (m, 2H), 7.12–7.28 (m, 3H), 7.40–7.52 (m, 3H), 7.79–7.85 (m, 2H). Anal. Calcd. for $C_{21}H_{21}N$: C, 87.80; H, 7.32; N, 4.88. Found: C, 87.63; H, 7.08; N, 4.67%.

Compound **11a** was aromatised with DDQ in refluxing benzene to furnish the fully aromatic analogue as a light yellow solid, mp 82–83 °C (chloroform–petroleum ether, 60–80 °C); δ_H ($CDCl_3$, 300 MHz): 1.03 (t, 3H, *J* 7.4 Hz), 1.53–1.66 (m, 2H), 1.77–1.87 (m, 2H), 3.60 (t, 2H, *J* 8.0 Hz), 7.59–7.64 (m, 1H), 7.69–7.88 (m, 5H), 8.03 (d, 1H, *J* 9.4 Hz), 8.27 (d, 1H, *J* 8.5 Hz),

8.38 (d, 1H, *J* 8.4 Hz), 9.54 (br d, 1H, *J* 7.7 Hz). Anal. Calcd. for $C_{21}H_{19}N$: C, 88.42; H, 6.67; N, 4.91. Found: C, 88.31; H, 6.43; N, 4.75%.

Selected data for 11c

δ_H ($CDCl_3$, 200 MHz): 0.84 (t, 3H, *J* 7.0 Hz), 1.26–1.33 (m, 4H), 1.60–1.68 (m, 2H), 2.96 (s, 3H), 3.32 (s, 3H), 3.88 (t, 1H, *J* 7.0 Hz), 7.04–7.08 (m, 1H), 7.15–7.18 (d, 1H, *J* 8.2 Hz), 7.22–7.30 (m, 5H), 7.53 (d, 1H, *J* 8.2 Hz), 7.61 (br d, 1H, *J* 8 Hz); δ_C: 13.94, 21.66, 22.74, 29.27, 43.42, 44.14, 46.67, 121.04, 122.65, 124.69, 126.29, 126.57, 126.64, 128.35, 129.09, 133.65, 134.20, 135.04, 135.25, 141.38, 147.04. Anal. Calcd. for $C_{23}H_{25}N$: C, 87.62; H, 7.94; N, 4.44. Found: C, 87.30; H, 7.59; N, 4.21%.

Selected data for 15a

δ_H ($CDCl_3$, 200 MHz): 0.81 (t, 3H, *J* 7.0 Hz), 1.19–1.33 (m, 4H), 1.77–1.88 (m, 2H), 3.81 (s, 3H), 4.77 (dd, 1H, *J* 7.4 and 4.6 Hz), 7.42–7.69 (m, 6H), 7.76–7.93 (m, 4H), 8.16 (2 × d merged to br t, 2H, *J* 9.3 and 8.7 Hz), 8.43 (d, 1H, *J* 8.4 Hz), 8.69 (d, 1H, *J* 7.7 Hz). Anal. Calcd. for $C_{30}H_{27}N$: C, 89.78; H, 6.73; N, 3.49. Found: C, 89.53; H, 6.49; N, 3.22%.

Selected data for 15b

δ_H ($CDCl_3$, 300 MHz): 1.40 (d, 3H, *J* 6.9 Hz), 5.00 (q, 1H, *J* 6.9 Hz), 6.93 (br s, 1H), 7.12 (d, 1H, *J* 8.6 Hz), 7.29 (t, 1H, *J* 7.4 Hz), 7.46–7.60 (m, 4H), 7.64 (d, 1H, *J* 8.6 Hz), 7.77–7.86 (m, 4H), 8.04 (d, 1H, *J* 8.5 Hz), 8.27 (d, 1H, *J* 8.5 Hz), 8.62 (d, 1H, *J* 8.2 Hz). Anal. Calcd. for $C_{26}H_{19}N$: C, 90.43; H, 5.51; N, 4.06. Found: C, 90.12; H, 5.27; N, 3.77%.

Acknowledgements

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References

1 T. W. Bell, P. J. Cragg, A. Firestone, D. I. Kwok, J. Liu, R. Ludwig and A. Sodoma, *J. Org. Chem.*, 1998, **63**, 2232.
2 T. R. Kelly, R. L. Xie, C. K. Weinreb and T. Bregant, *Tetrahedron Lett.*, 1998, **39**, 3675.
3 J. Pataki, H. Lee and R. G. Harvey, *Carcinogenesis*, 1983, **4**, 399.
4 G. Boisvert and R. Giasson, *Tetrahedron Lett.*, 1992, **33**, 6587.
5 D. J. Pippel, M. D. Curtis, H. Du and P. Beak, *J. Org. Chem.*, 1998, **63**, 2.
6 G. K. Kar, I. Sami and J. K. Ray, *Chem. Lett.*, 1992, 1739.
7 G. K. Kar, A. C. Karmakar and J. K. Ray, *Tetrahedron Lett.*, 1989, **30**, 223.
8 M. Ishikawa and S. Fukuzumi, *J. Am. Chem. Soc.*, 1990, **112**, 8864.