Synthesis of Novel Anthrone Imines

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Introduction

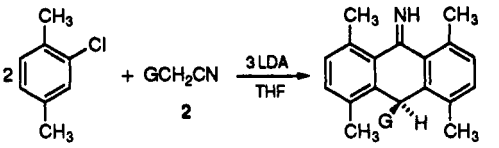
We[1] recently reported a stereocontrolled synthesis of *cis*-3,4-diaryl-8-methoxy-5-methylisochroman-1-ones (isocoumarins), which involves trapping 2-(α-lithioarylmethyl)-6-methoxy-3-methylbenzonitriles with benzaldehydes, and allowing the lithiated *anti*-1,2-diaryl-2-(2′-cyano-3′-methoxy-6′-methylphenyl)ethanols so formed to cyclize diastereospecifically to the corresponding *cis*-3,4-diaryl-8-methyl-5-methoxyisocoumarins. The (α-lithioarylmethyl)benzonitriles are prepared *in situ* by the reaction of 2-bromo-4-methylanisole and arylacetonitriles with lithium diisopropylamide (LDA) in tetrahydrofuran (THF), presumably by a tandem addition–rearrangement pathway.[2] We subsequently attempted to extend this methodology to the preparation of *cis*-3,4-diphenyl-5,8-dimethylisocoumarins by trapping the lithiated rearranged nitrile from the reaction of 2-bromo-1,4-dimethylbenzene (1), (4-methoxyphenyl)acetonitrile (**2b**), and LDA with benzaldehyde. However, the expected *cis*-3,4-diarylisochroman-1-one was not obtained, but rather a novel imine derivative of 9(10*H*)-anthracenone (hereafter referred to as anthrone), i.e. 10-(4′-methoxyphenyl)-1,4,5,8-tetramethylanthrone imine (**3b**), was isolated, along with the rearranged product, 2-(4′-methoxyphenyl)-3,6-dimethylbenzonitrile. The structure of the imino derivative **3b** was confirmed by single crystal X-ray crystallography.[3]

Results and Discussion

We have repeated the reaction of **1** (2 equiv) and a variety of arylacetonitriles (**2a–f**) (1 equiv) and thiopheneacetonitriles (**2g,h**) with LDA (3 equiv), and using the usual methanol quench in the reaction workup, obtained the corresponding anthrone imine **3** in fair to good yields (42–81%). The results are shown in Table 1. ^{1}H and ^{13}C NMR spectroscopy, HRMS, and elemental analyses were consistent with the proposed structures of **3a–h**. For example, the mass spectrum of these compounds all exhibited a 248 *m/e* peak corresponding to the loss of the 10-aryl group from the parent ion, the ^{13}C NMR spectra revealed a C=N resonance at 172.5–175 ppm, and the ^{1}H NMR spectra showed a resonance at δ 5.40–6.40 ppm corresponding to the 10-H.

A possible pathway for the formation of the **3** from the reaction of **1** and **2** is shown in Scheme 1. Thus, the α-lithiated nitrile (**2′**) adds to 3,6-dimethylbenzyne (**4**) to give adduct **5**, which cyclizes to the benzocyclobutanamine intermediate **6**. Ring opening of **6** supplies the rearranged ion **7**, which undergoes a 4 + 2 cycloaddition with another molecule of benzyne **4** to yield **3**, after proton quench of the resulting N-lithiated imine derivative **8**.

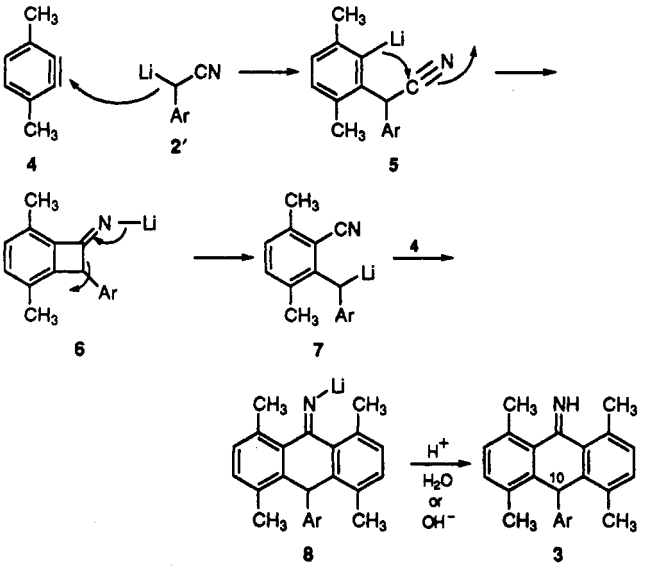
Table 1. Preparation of Anthrone Imines 3



1 3

entry	nitrile	G	imine	yield, %
1	**2a**	C_6H_5	**3a**	72
2	**2b**	2-MeO-C_6H_4	**3b**	66
3	**2c**	3-MeO-C_6H_4	**3c**	81
4	**2d**	4-MeO-C_6H_4	**3d**	65
5	**2e**	1-naphthyl	**3e**	63
6	**2f**	3,4-$(MeO)_2C_6H_3$	**3f**	42
7	**2g**	2-thiophene	**3g**	64
8	**2h**	3-thiophene	**3h**	72

Scheme 1



Interestingly, tautomerization of **3** to the more common 9-amino form was not detected. Also, these imines not only failed to hydrolyze to anthrones during the aqueous reaction workup, but also resisted hydrolysis when refluxed for 36 h in either 20% methanolic HCl or 30% ethanolic NaOH. We have carried out AM1 molecular orbital calculations[4] on both 10-phenyl-1,4,5,6-tetramethylanthracene tautomers. The lowest energy conformer of the imino tautomer was computed to have the butterfly structure shown in Figure 1. Somewhat surprisingly this conformation permits an almost complete elimination of steric congestion between the 10-phenyl and flanking methyl groups. Thus, comparison of the computed heat of formation with those of the unsubstituted parent and its tetramethyl derivative suggests a residual steric strain associated with insertion of the 10-phenyl group of less than 1 kcal mol^{-1}. The situation is quite different for the 9-amino tautomer which was computed to be 13 kcal mol^{-1} less stable than the imino form. Here, accommodation of the approximately trigonal hybridization at C-10 forces the attached phenyl group into a highly unfavorable steric environment which is only partially alleviated by distortion

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(2) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178.
(3) Biehl, E. R.; Dutt, M.; Fravel, B.; Zhang, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1520.
(4) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

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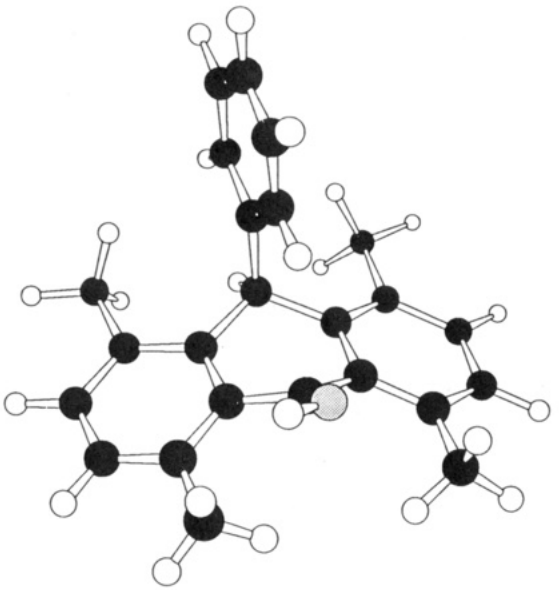

Figure 1. AM1 structure of the most stable conformer of the imino tautomer.

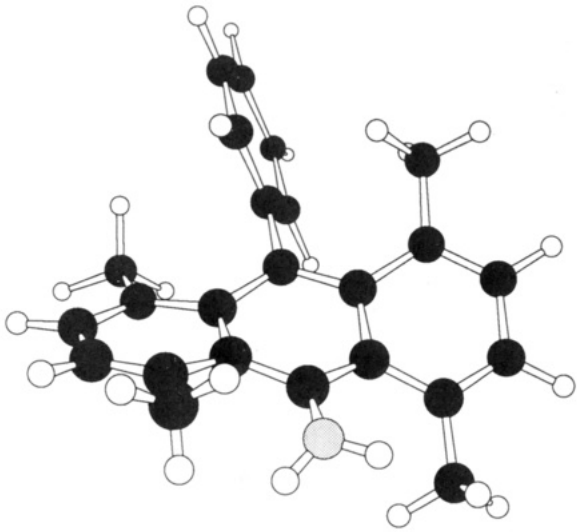

Figure 2. AM1 structure of the amino tautomer.

of the anthracene skeleton into the propeller conformation and rotation about the bond to the 10-phenyl group (Figure 2). In the search for further insight into the role played by these unfavorable steric interactions we also carried out a similar study of the 10-*tert*-butyl analogs where, of course, the latter avenue for relief of such strain is absent. Not unexpectedly the energetic preference for the imino tautomer was computed to be even greater (25.0 kcal mol^{-1}). While we have not studied the hydrolysis pathway in detail, inspection of the computed geometry of the imino tautomer of 10-phenyl-1,4,5,6-tetramethylanthracene supports the supposition that its resistance to hydrolysis is associated with steric hindrance to attack of water to the intermediate iminium ion.

Experimental Section

Melting points were determined on an electrothermal apparatus and are uncorrected. All glassware was dried prior to use and the reactions were carried out under a N_2 atmosphere. NMR chemical shifts were related to TMS as an internal standard. All reagents were purchased from Aldrich Chemical Co. The nitriles were distilled prior to use, *n*-butyllithium was used as received, and THF was freshly distilled from sodium benzophenone ketyl. 2-Bromo-1,4-dimethylbenzene was prepared by treating 1,4-dimethylbenzene with NBS in DMF at rt.

The AM1 calculations and subsequent visualization of the optimized structures was carried out on a Silicon Graphics, Inc. INDIGO workstation using version 3 of SPARTAN.[5]

General Procedure for the Aryne Reaction 2-Bromo-1,4-dimethylbenzene (1) and Arylacetonitriles 2 with LDA in THF. In a flame-dried flask flushed with nitrogen, 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 THF at −78 °C under a nitrogen atmosphere. After 10 min at −78 °C, the appropriate nitrile (10 mmol) in THF (40 mL) was added dropwise over 20 min and the reaction mixture was stirred an additional 10 min at −78 °C. The mixture was then warmed to −40 °C, 1 (10 mmol) in 10 mL of THF was added dropwise over a period of 10 min, and the mixture was allowed to warm to rt. The resulting dark reddish solution was quenched with methanol (2 mL), the THF was evaporated (rotatory evaporator), and the residue was 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 to 9:1, depending upon the polarity of the product) as eluent. The physical and spectral properties of the compounds isolated in pure form are shown below.

1,4,5,8-Tetramethyl-10-phenylanthrone Imine (3a): colorless solid, mp 183–184 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 6 H), 2.60 (s, 6 H), 5.50 (s, 1 H), 7.08 (s, 7 H), 7.15–7.17 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 19.6, 20.48, 44.5, 126.1, 128.4, 129.0, 130.8, 132,7, 132.8, 136.6, 139.8, 141.6, 173.6. Anal. Calcd for $C_{24}H_{23}N$: C, 88.57; H, 7.12; N, 4.30. Found: C, 88.65; H, 7.16; N, 4.32.

1,4,5,8-Tetramethyl-10-(2′-methoxyphenyl)anthrone Imine (3b): colorless solid, mp 249–252 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 6 H), 2.61 (s, 6 H), 3.90 (s, 3 H), 5.97 (s, 1 H), 6.82–7.03 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 19.7, 20.9, 37.8, 55.1, 110.6, 121.3, 127.4, 129.7, 130.0, 130.6, 131.0, 132.5, 133.6, 136.7, 140.9, 155.8, 174.8; HRMS calcd for $C_{25}H_{25}NO$ 355.1940, found 355.1936. Anal. Calcd for $C_{25}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.96; H, 7.36; N, 4.12.

1,4,5,8-Tetramethyl-10-(3′-methoxyphenyl)anthrone Imine (3c): mp 218–219 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 6 H), 2.54 (s, 6 H), 3.67 (s, 3 H), 5.51 (s, 1 H), 6.65–6.70 (m, 2 H), 7.05–7.09 (m, 6 H), 7.24 (s, 1 H); HRMS calcd for $C_{25}H_{25}NO$ 355.1940, found 355.1932. Anal. Calcd for $C_{25}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.86; H, 7.37; N, 4.10.

1,4,5,8-Tetramethyl-10-(4′-methoxyphenyl)anthrone Imine (3d): colorless crystals, mp 217–220 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6 H), 2.59 (s, 6 H), 3.67 (s, 3 H), 5.44 (s, 1 H), 6.65–6.70 (m, 2 H), 7.05–7.09 (m, 6 H), 7.24 (s, 1 H). Anal. Calcd for $C_{25}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.87; H, 7.39; N, 4.07.

1,4,5,8-Tetramethyl-10-(3′,4′-methoxyphenyl)anthrone Imine (3e): thick liquid; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 6 H), 2.64 (s, 6 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 5.60 (s, 1 H), 6.72 (dd, J = 6 Hz, 2 H), 6.80 (s, 2 H), 7.11 (s, 2H), 7.27 (s, 2 H); HRMS calcd for $C_{26}H_{27}NO_2$ 385.20417, found 385.20307. Anal. Calcd for $C_{26}H_{27}NO_2$: C, 82.01; H, 7.06; N, 3.63. Found: C, 81.99; H, 7.01; N, 3.73.

1,4,5,8-Tetramethyl-10-(1′-naphthyl)anthrone Imine (3f): colorless crystals, mp 336–338 °C; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6 H), 2.63 (s, 6 H), 6.22 (s, 1 H), 6.28–7.73 (m, 11 H), 8.76 (d, J = 2.7 Hz, 1 H); HRMS calcd for $C_{28}H_{25}N$ 375.1987, found 375.1982. Anal. Calcd for $C_{28}H_{25}N$: C, 89.56; H, 6.71; N, 3.73. Found: C, 89.60; H,6.77; N, 3.73.

1,4,5,8-Tetramethyl-10-(2′-thienyl)anthrone Imine (3g): colorless crystals, mp 205–206 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 6 H), 2.55 (s, 6 H), 5.71 (s, 1 H), 6.48–6.51 (m, 1 H), 6.70–6.73 (m, 1 H), 6.93–6.95 (m, 1 H), 7.06 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.2, 20.3, 39.6, 123.9, 124.9, 126.4, 130.2, 130.9, 132.0, 132.9, 136.5, 139.3, 145.9, 172.6. HRMS calcd for $C_{22}H_{21}NS$ 351.1394, found

(5) SPARTAN, Wavefunction, Inc., 18401 on Karman, #370, Irvine, CA 92715.

351.1386. Anal. Calcd for $C_{22}H_{21}NS$: C, 79.72; H, 6.39; N, 4.23. Found: C, 79.81; H, 6.36; N, 4.24.

1,4,5,8-Tetramethyl-10-(3′-thienyl)anthrone Imine (3h): colorless crystals, mp 219–221 °C; ^1H NMR ($CDCl_3$) δ 2.60 (s, 6 H), 2.72 (s, 6 H), 5.70 (s, 1 H), 6.60–6.75(m, 2 H), 7.70 (m, 6 H); HRMS calcd for $C_{22}H_{21}NS$ 351.1394, found 351.1395. Anal. Calcd for $C_{22}H_{21}NS$: C, 79.72; H, 6.39; N, 4.23. Found: C, 79.71; H, 6.31; N, 4.27.

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