

A Novel Synthesis of the Fluorene Skeleton

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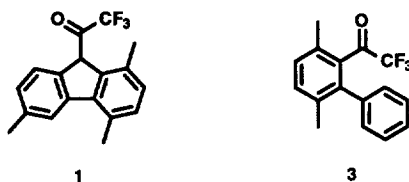
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Summary: 1,4,6-Trimethyl-9-trifluoroacetylfluorene **1** has been synthesized in one pot from 2-chloro-*p*-xylene **2** and has been characterized by single-crystal X-ray diffraction.

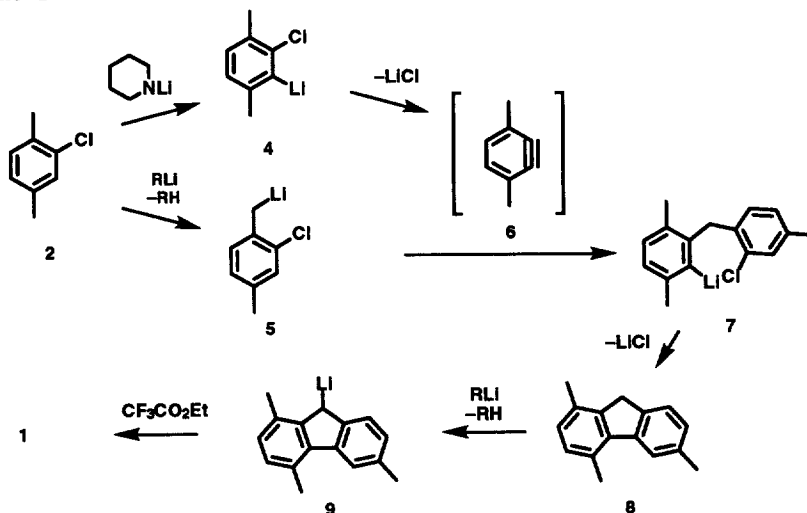
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Lithium piperidide in ether has been reported to be a better benzyne-producing reagent than phenyllithium, whereas the generated benzyne, given a choice, reacts preferentially with phenyllithium over piperidide.¹ However, a 1 : 1 mixture of the two reagents in tetrahydrofuran (THF), when treated sequentially with 2-chloro-*p*-xylene² (**2**) and then ethyl trifluoroacetate, afforded the substituted fluorene **1** in 82% yield, rather than the expected 3,6-dimethyl-2-phenyl- α,α -trifluoroacetophenone **3**.³

This result can be rationalized by the series of reactions shown in Scheme 1. If competitive deprotonations take place at position 3 and at the benzylic position of **2**, to yield **4** and **5**, respectively, **4** can generate benzyne **6**, which then reacts preferentially with **5**, rather than with either phenyllithium or lithium piperidide. The other benzylic position of **2** is not deprotonated, since no 1,4,7-trimethylfluorene isomer of **1** has been observed. This suggests that the formation of **5** is favored by complexation effects involving lithium and the *ortho*-chlorine atom,



Scheme 1



analogous to acceleration of ortho metallation by fluorine or alkoxy groups.⁴ The addition product **7** then cyclizes and the resulting fluorene **8** (which is the most acidic product in the mixture) is deprotonated at position 9 to yield an anion (**9**) which after treatment with trifluoroacetic anhydride or (better) with ethyl trifluoroacetate forms the substituted fluorene **1**.

The product **1** was characterized by single-crystal X-ray diffraction (Figure 1).^{5,6}

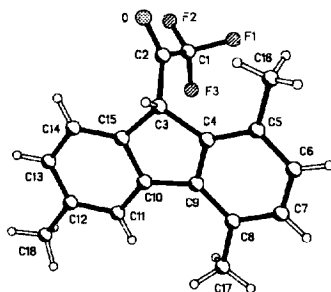


Figure 1. X-Ray structure of product **1**.

References and Notes:

- Huisgen, R.; Mack, W.; Möbius, L. *Tetrahedron* **1960**, *9*, 29-39.
- Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*, Academic Press, New York **1967**, p. 107.
- A typical procedure is as follows: lithium piperidide was made at $-40\text{ }^{\circ}\text{C}$ (dry ice/acetonitrile bath) in 5 mL tetrahydrofuran from piperidine (1.0 mL, 10.1 mmol, 0.9 equiv) and *n*-butyllithium (5.0 mL of 2.0 M solution in hexanes; 10.0 mmol, 0.9 equiv). The mixture was stirred for 15 min at $-40\text{ }^{\circ}\text{C}$ after which phenyllithium (8.0 mL of 1.82 M solution in cyclohexane/ether 7 : 1; 14.6 mmol, 1.3 equiv) was added to the milky white suspension, followed by 5 mL tetrahydrofuran. 2-Chloro-*p*-xylene (solution in 10 mL tetrahydrofuran; 1.50 mL, 11.2 mmol, 1 equiv) was added in one portion and the solution was stirred at $0\text{ }^{\circ}\text{C}$. The initial color slowly changed to a much darker, almost black color. The solution was stirred for 35 h at $0\text{ }^{\circ}\text{C}$ and was cannulated into a precooled ($-78\text{ }^{\circ}\text{C}$) solution of trifluoroacetic anhydride (3.1 mL, 22 mmol, 2.0 equiv) in 15 mL tetrahydrofuran over a 20-min period. Concentration to dryness was followed by dilution with 30 mL ether. The organic layer was washed with 12M HCl until the aqueous layer became almost colorless. The organic layer was neutralized with 5% sodium carbonate and dried with brine and over MgSO_4 , then concentrated. Silica gel chromatography (hexanes) afforded **1** in 82% yield (1.36 g = 4.6 mmol); FTIR (thin film) 3041, 3020, 2972, 2959, 2926, 1738, 1609, 1463, 1447; ^1H NMR (CDCl_3 , 500 MHz) δ 2.27 (6H, s), 2.48 (3H, s), 2.71 (3H, s), 5.13 (1H, s), 7.06 (1H, d, $J = 7.6$ Hz), 7.16 (1H, d, $J = 7.8$ Hz), 7.17 (1H, d, $J = 7.8$ Hz), 7.39 (1H, d, $J = 7.7$ Hz), 7.76 (1H, s); MS (EI⁺) m/z 304 (33) $[\text{M}]^+$, 235 (5), 207 (100).
- (a) Brandsma, L.; Verkruisje, H. D. *Preparative Polar Organometallic Chemistry*, Springer, Berlin, **1987**, vol. 1, p. 30 and references therein. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
- A triclinic crystal was obtained from dichloromethane at $+20\text{ }^{\circ}\text{C}$; space group *P*1. A total of 8561 reflections were collected at $+20\text{ }^{\circ}\text{C}$; unit cell dimensions $a = 8.981(3)\text{ \AA}$, $b = 9.673(3)\text{ \AA}$, $c = 9.949(2)\text{ \AA}$; $\alpha = 94.40(2)^{\circ}$, $\beta = 101.45(2)^{\circ}$, $\gamma = 115.76(2)^{\circ}$; $Z = 2$. Least squares refinement against F^2 using all data converged on the structure shown in Figure 1 with wR^2 (F^2 , all data) = 0.2660, R (conventional) = 0.0751 and a goodness of fit on F^2 of 0.894.
- Thanks are due to the National Institutes of Health and the National Science Foundation for financial support.