Pergamon

Tetrahedron Letters 42 (2001) 3053–3056

TETRAHEDRON LETTERS

A facile one-pot synthesis of polysubstituted naphthalenes

Alexander S. Kiselyov*

Department of Chemistry, ImClone Systems, Inc., 180 Varick Street, 6th Floor, New York, NY 10014, USA

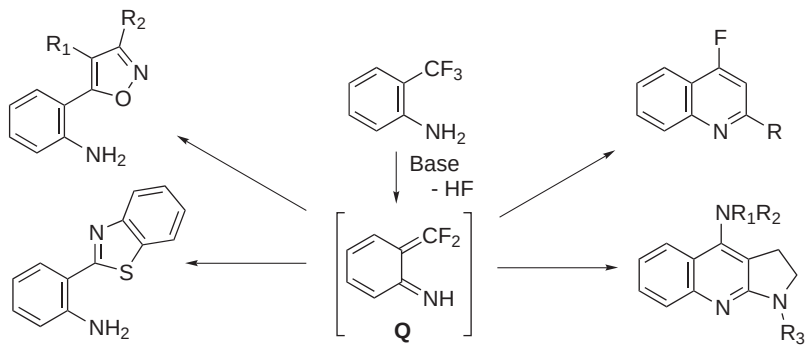
Received 20 February 2001; accepted 5 March 2001

Abstract—Synthesis of the title compounds from (2-trifluoromethyl)phenylacetonitrile is described. The mechanism of the reaction is believed to involve the formation of the quinone methide intermediate.

The anionically activated trifluoromethyl group has great utility in the synthesis of various aromatic and heteroaromatic compounds, such as syntheses of 2-(substituted 1-alkenyl) anilines,[2] 2-substituted benzothiazoles and benzoxazoles,[3] 4(5)-dihydro-1*H*-imidazole,[4] triazines,[5] and isoxazoles,[5] 1,3-disubstituted naphthalenes,[6] 2,4-di- or 2,3,4-trisubstituted quinolines,[7] 7-(substituted amino)-5,6-dihydrobenz[*c*]acridines,[8] 4-fluoroquinolines,[9] and fused fluoronaphthalenes.[10] A relevant synthesis of 3-aryl-4-aminocinnolines has been reported recently.[11] Representative examples of this chemistry are summarized in Scheme 1. It has been suggested that all of the above transformations proceed via the initial proton abstraction from the anilinic nitrogen to afford the quinone methide intermediate **Q** (Scheme 1). Subsequent reaction of this intermediate with various nucleophiles may lead to the observed array of products. Studies on the base-induced conversions of derivatives of *ortho*-trifluoromethyl toluene have been published.[10]

In this paper, we report the facile synthesis of 1,2,3,4-tetrasubstituted naphthalenes via the condensation of 2-trifluoromethylphenyl acetonitrile (**1**) with aromatic acetonitriles under basic conditions. In the initial experiment, **1** undergoes a facile self-condensation reaction under basic conditions to afford 1-fluoro-2-aryl-3-amino-4-cyanonaphthalene (**2**). The yields of **2** varied dramatically depending on the reaction conditions (Scheme 2).

In order to optimize the yield of **2**, we studied the effects of several factors on the outcome of this reaction including: (i) reaction temperature; (ii) ratio of substrate (**1**) to base; (iii) reaction time; (iv) solvent, and (v) nature of base. Some of these studies are summarized in Scheme 2. Temperature was found to have a profound effect on the reaction course. For example, treatment of **1** with 1 equiv. of LDA in THF at −78°C for 24 h, followed by aqueous quenching of the reaction mixture with water, afforded only the starting material in quantitative yield. Similar treatment of **1** at −30°C (MeCN/ethylene glycol/dry ice mixture) for 12 h furnished **2** in 23% yield along with the starting material **1** (66%). A

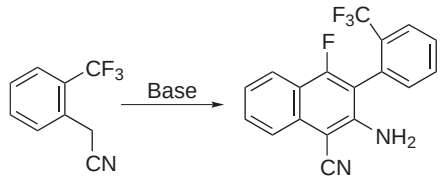


Scheme 1.

Keywords: naphthalenes; fluorine and compounds; condensations.

* Fax: (212) 645-2054; e-mail: alexanderk@imclone.com

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00373-2



1 2

Reaction conditions:

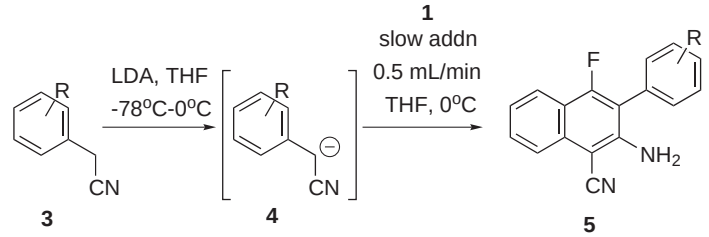
Base	Ratio **1**/base	Solvent	Temperature, °C	Rxn time, h	Yield of **2**, %[a]
LDA	1	THF	-78 to -60	24	no rxn
LDA	1	THF	-30	12	23
LDA	1	THF	-10 to 0	12	26
LDA	1	THF	RT	10	18
LDA	2	THF	-30	12	32
LDA	2	THF	-10 to 0	12	30
LDA	**4**	**THF**	**-30**	**12**	**57**
LDA	6	THF	-30	12	53
LiTMP[b]	4	THF	-30	12	52
LiHMDS[c]	4	THF	-30	12	53
NaHMDS	4	THF	-30	12	48
EtMgBr	4	THF	-30	8	23
EtO^-	6	EtOH	RT to reflux	14	37

[a]Yield refers to isolated **2**; [b]TMP = 2,2,6,6-tetramethylpiperidiene; [c]HMDS = 1,1,1,3,3,3-hexamethyldisilazane

Scheme 2.

further increase in the reaction temperature to 0°C did not affect the yield of **2**. A significant decrease in the yield of **2** (18%), as well as the formation of unidentified high-molecular weight products, was observed when the reaction was conducted at ambient temperature. The optimal ratio of **1** to base was found to be 1:4. Lower ratios resulted in lower yields of **2**, higher ratios (6–8) did not significantly affect the reaction outcome. THF and dimethoxyethane (DME) were efficacious solvents for the reaction (54–57% yields of **2**), whereas reactions conducted in diethyl ether afforded only 25–29% yield of **2**. Several amide bases, including LDA, LiTMP (2,2,6,6-tetramethylpiperidide), and LiHMDS (1,1,1,3,3,3-hexamethyldisilazide), furnished essentially similar yields of **2** (48–53%). The nature of the cation did not affect the yield. Interestingly, this reaction was also promoted by EtMgBr, although a number of side products were detected in the reaction mixture along with **2** (23% isolated yield). Application of NaOEt in refluxing EtOH (6 equiv.) also furnished **2**, albeit in lower yields (37%) when compared with lithium amides. Reaction times of 12–13 h were essential to assure the complete conversion of **1** to **2** at −30°C. The optimized reaction conditions are indicated in Scheme 2 (bold captions).[12]

The development of the reaction protocol for the self-condensation reaction of **1** allowed us to attempt a similar transformation involving **1** and anions derived from aromatic acetonitriles. To our satisfaction, addition of **1** to a solution of **4** (2 molar equiv.) and LDA (2 molar equiv.) allowed for a smooth condensation

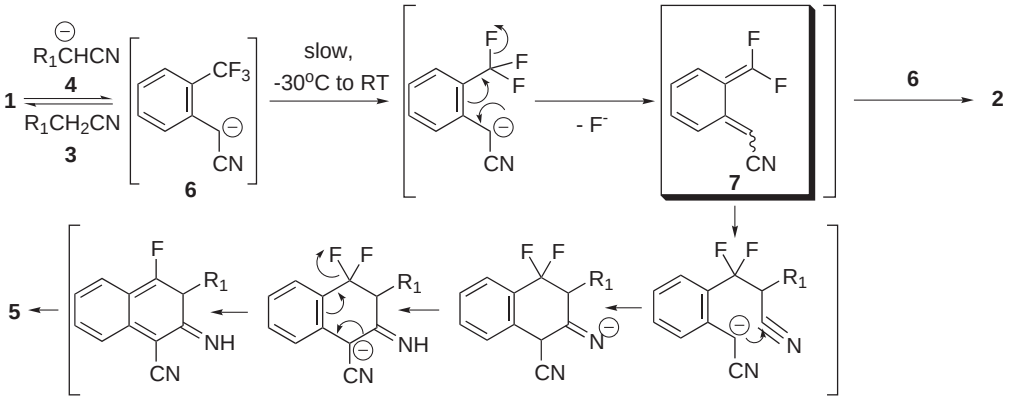


3 4 5

	R	Yield, %[a]		R	Yield, %[a]
a	2-Me	65	**e**	4-OMe	61
b	3-Me	67	**f**	2-F	68
c	2-OMe	63	**g**	3-F	47
d	3-OMe	49	**h**	4-F	50

[a]Yields refer to isolated, analytically pure **5**

Scheme 3.



Scheme 4.

reaction to afford **5** in 49–68% isolated yields (Scheme 3).[13]

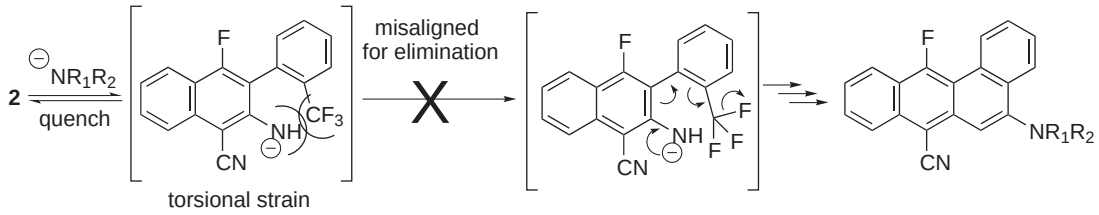
Varying amounts of **2** (5–15%) were detected in the reaction mixtures. The desired products **5** were easily separated by column chromatography. The optimal rate of addition of **1** (0.01 M solution in THF) to **4** (0.01 M solution in THF) was 0.25–0.5 mL/min. Faster addition rates, application of a more concentrated solution of **1**, or lower reaction temperatures resulted in the formation of significant amounts of self-condensation product **2** (25–95%!). When higher equivalents of **4** were used to facilitate the reaction, the isolation of the targeted naphthalenes was somewhat cumbersome, while the overall yield of **5** was not affected significantly.[14]

The reported observations can be rationalized by the mechanism presented in Scheme 4. It involves the initial deprotonation of **1** to form **6**, which is stable at temperatures below −30°C. At higher temperatures the anion **6** undergoes slow elimination of HF to form the quinone methide intermediate **7**. These active species react with **6** to afford the self-condensation product **2** after a series of addition/elimination steps. Alternatively, **7** reacts with an excess of **4** to afford **5**. Indirect support to this mechanism is provided by the fact that both the dilution of the reaction mixture, as well as the slow addition of the substrate **1** (to assure a large excess of **4** over **1**, and consequently **6**), dramatically improve the yields of **5** versus the self-condensation product **2**. Additionally, higher reaction temperatures allow for the facile elimination of F^- from **6**, shifting the overall equilibrium of the reaction towards the formation of the key reactive intermediate **7**. Formation of a similar quinone methide intermediate was suggested in several relevant transformations of (2-trifluoromethyl)aniline.[1]

In summary, we have described a protocol for the rapid assembly of 1,2,3,4-tetrasubstituted naphthalenes from 2-(trifluoromethyl)phenylacetonitrile and aromatic acetonitriles. The proposed reaction mechanism for this reaction involves the formation of the quinone methide intermediate. Detailed mechanistic studies of this reaction are in progress in our lab.

References

1. Kiselyov, A. S.; Strekowski, L. *Org. Prep. Proc. Int.* **1996**, *28*, 289 and references cited therein.
2. Hojjat, M.; Kiselyov, A. S.; Strekowski, L. *Synth. Commun.* **1994**, *24*, 267.
3. Kiselyov, A. S.; Hojjat, M.; Van Aken, K.; Strekowski, L. *Heterocycles* **1994**, *37*, 775.
4. Wydra, R.; Patterson, S. E.; Strekowski, L. *J. Heterocyclic Chem.* **1990**, *27*, 803.
5. Strekowski, L.; Lin, S.-Y.; Nguyen, J.; Redmore, N.; Mason, J. C.; Kiselyov, A. S. *Heterocyclic Commun.* **1995**, *1*, 331.
6. Strekowski, L.; Wydra, R.; Kiselyov, A. S.; Baird, J. H. *Synth. Commun.* **1994**, *24*, 257.
7. (a) Strekowski, L.; Patterson, S. E.; Janda, L.; Wydra, R.; Harden, D. B.; Lipowska, M.; Cegla, M. *J. Org. Chem.* **1992**, *57*, 196; (b) Janda, L.; Nguyen, J.; Patterson, S. E.; Strekowski, L. *J. Heterocyclic Chem.* **1992**, *29*, 1753.
8. Strekowski, L.; Wydra, R.; Harden, D. B.; Honkan, V. A. *Heterocycles* **1990**, *31*, 1565.
9. Strekowski, L.; Kiselyov, A. S.; Hojjat, M. *J. Org. Chem.* **1994**, *59*, 5886.
10. Kiselyov, A. S.; Strekowski, L. *Tetrahedron Lett.* **1994**, *35*, 7597.
11. Kiselyov, A. S. *Tetrahedron Lett.* **1995**, *36*, 1383.
12. The subsequent cyclization of **2** was not successful under a variety of experimental conditions, including prolonged stirring of **2** with a 10–20 fold excess of LDA or NaHMDS in THF at room temperature. Only unreacted starting material was recovered from the reaction mixtures in almost quantitative yield. This result could be explained by the fact that the CF_3 group in the intermediate *N*-centered anion is misaligned for the elimination of F^- due to severe torsional strain (Scheme 5).
13. **Typical experimental procedure**: A solution of 2-(trifluoromethyl)phenylacetonitrile (**1**) (185 mg, 1 mmol) in 100 mL of dry THF was added via funnel at the rate of 0.25 mL/min to a vigorously stirred mixture of aryl-



Scheme 5.

acetonitrile (2 mmol) and LDA (4 mmol, freshly prepared from diisopropylamine and *n*-BuLi) in 200 mL of dry THF at 0°C under Ar. After the addition was finished (6–7 h), the dark yellow reaction mixture was warmed to room temperature and stirred for an additional 4 h. The resulting solution was concentrated in vacuo, the residue was partitioned between EtOAc and concentrated aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (silica gel, hexane/EtOAc = 2:1) to afford the analytically pure naphthalene **5**.

14. Yields refer to the isolated analytically pure compounds. Representative examples:
Compound **2**: mp 183°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.16 (br s, 2H, exch. D_2O, NH_2), 7.26 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.52–7.61 (m, 2H), 7.65–7.72 (m, 2H), 7.74–7.85 (m, 2H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −112.9, −60.6. ESI MS: (M+1) 331, (M−1) 329. Elemental analysis calcd for $C_{18}H_{10}F_4N_2$: C, 65.46; H, 3.05; N, 8.48. Found: C, 65.37; H, 3.11; N, 8.33.
Compound **5c**: 51% yield, mp 187°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.74 (s, 3H, OMe), 5.96 (br s, 2H, exch. D_2O, NH_2), 7.08 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −114.2; ESI MS: (M+1) 293, (M−1) 291. Elemental analysis calcd for $C_{18}H_{13}FN_2O$: C, 73.96; H, 4.48; N, 9.58. Found: C, 73.73; H, 4.58; N, 9.36.
Compound **5d**: 49% yield, mp 158°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H, OMe), 4.82 (br s, 2H, exch. D_2O, NH_2), 6.92 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H); ^{19}F NMR (400 MHz, DMSO-d_6): δ −115.5; ESI MS: (M+1) 293, (M−1) 291. Elemental analysis calcd for $C_{18}H_{13}FN_2O$: C, 73.96; H, 4.48; N, 9.58. Found: C, 73.81; H, 4.52; N, 9.51.
Compound **5e**: 55% yield, mp 188°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, OMe), 6.02 (br s, 2H, exch. D_2O, NH_2), 7.14 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H); ^{19}F (400 MHz, DMSO-d_6): δ −115.7; ESI MS: (M+1) 293, (M−1) 291. Elemental analysis calcd for $C_{18}H_{13}FN_2O$: C, 73.96; H, 4.48; N, 9.58. Found: C, 73.83; H, 4.56; N, 9.48.