Registry No. $PhNO_2$, 98-95-3; m-$CH_3C_6H_4NO_2$, 99-08-1; m-$ClC_6H_4NO_2$, 121-73-3; m-$HO_2CC_6H_4NO_2$, 121-92-6; m-$CH_3OC_6H_4NO_2$, 555-03-3; m-$FC_6H_4NO_2$, 402-67-5; m-$IC_6H_4NO_2$, 645-00-1; m-$NCC_6H_4NO_2$, 619-24-9; p-$O_2NC_6H_4NH_2$, 100-01-6; 2-CH_3-4-$O_2NC_6H_3NH_2$, 99-52-5; 2-Cl-4-$O_2NC_6H_3NH_2$, 121-87-9; 2-H_2N-5-$O_2NC_6H_3CO_2H$, 616-79-5; 2-CH_3O-4-$O_2NC_6H_3NH_2$, 97-52-9; 2-F-4-$O_2NC_6H_3NH_2$, 369-35-7; 2-I-4-$O_2NC_6H_3NH_2$, 6293-83-0; 2-NC-4-$O_2NC_6H_3NH_2$, 17420-30-3; 4-amino-1,2,4-triazole, 584-13-4.

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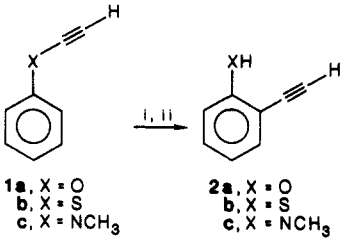
Halocarbon Chemistry. 3. Ortho Metallation-Induced Cyclization of Acetylenes: One-Flask Synthesis of 2,3-Disubstituted Benzofurans, Thianaphthenes, and Indoles

Summary: A new base-induced cyclization is described which involves the direct one-pot conversion of trifluoroethyl phenyl ethers, thioethers, and amines, in the presence of 4 equiv of alkyl- or aryllithium reagents, to 2,3-disubstituted benzofurans, thianaphthenes, and indoles, respectively.

Sir: Previously we have reported[1] an unprecedented anionic rearrangement of (aryloxy)acetylenes **1a** to the corresponding *o*-ethynylphenols **2** (Scheme I). More recently we have been able to effect the analogous reactions[2] with the corresponding sulfides **1b** and the *N*-alkylamines **1c**. However in the latter two cases the presence of a 2-bromo or a 3-methoxy group in the starting material is required to facilitate ortho deprotonation by the alkyllithium reagent. Preliminary mechanistic investigations in the case of **1a** led us to propose that the reaction proceeds by an anionic intramolecular attack of the *o*-lithio group on the lithioethynyl group. This leads to the rearranged product **2**, seemingly through an intermediate 2,3-dilithiobenzofuran. We believe that the rearrangements of the related sulfur and nitrogen compounds **1b** and **1c** proceed analogously through the 2,3-dilithiothianaphthenes and -indoles, respectively. These reactions suggested to us that a similar internal anionic attack on a disubstituted acetylene in a compound such as **4a**, might lead[3] via **4b** to anion **5**, and after quenching, to the corresponding 3-substituted and 2,3-disubstituted heterocycles (X = O, S, or NR) **6** and **7**, respectively, as shown in Scheme II. We now wish to report that investigations based on such speculation have led to the successful one-pot syntheses of benzofurans, thianaphthenes, and indoles.

In our preliminary work we selected the phenyl 2,2,2-trifluoroethyl ethers **3** (X = O) (easily prepared[4] from the sodium phenoxide and 2,2,2-trifluoroethyl tosylate) as the starting materials because of their known[4] concomitant dehalogenation and alkylation by 3 equiv of an alkyllithium (RLi) to acetylenes **4a** (X = O). We have now found that addition of a fourth equivalent of the alkyllithium reagent apparently generates anion **4b** (X = O), which cyclizes[5] to **5** (X = O), because, when the reaction mixture is proton-quenched, the corresponding 3-substituted benzofuran **6** (X = O) is obtained. Alternatively, quenching with a nonprotic electrophile (E) gives the 2,3-disubstituted benzofuran **7** (X = O).[5]

Scheme I[a]



1a, X = O
b, X = S
c, X = NCH_3

2a, X = O
b, X = S
c, X = NCH_3

[a] Reagents: (i) 2BuLi/THF/−78 °C to 25 °C; (ii) H_2O.

Scheme II

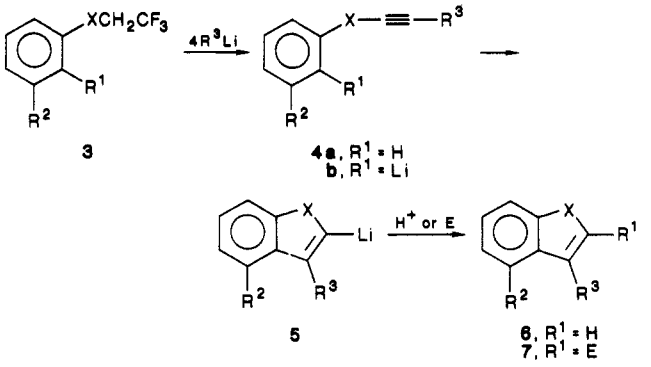


Table I[9-11]

item	substrate **3**	product **6** or **7**	yield, %
1	X = O, R^1 = R^2 = H	**6a**, R^2 = H, R^3 = *n*-Bu	40
2	X = O, R^1 = R^2 = H	**6b**, R^2 = H, R^3 = *sec*-Bu	40
3	X = O, R^1 = R^2 = H	**6c**, R^2 = H, R^3 = Pr	40
4	X = O, R^1 = R^2 = H	**7a**, R^2 = H, R^3 = *n*-Bu, E = I	30
5	X = S, R^1 = Br, R^2 = H	**6d**, R^2 = H, R^3 = *n*-Bu	40
6	X = S, R^1 = Br, R^2 = H	**6e**, R^2 = H, R^3 = *sec*-Bu	40
7	X = S, R^1 = Br, R^2 = H	**6f**, R^2 = H, R^3 = C_6H_5	60
8	X = S, R^1 = Br, R^2 = H	**7b**, R^2 = H, R^3 = *n*-Bu, E = I	40
9	X = NCH_3, R^1 = H, R^2 = OCH_3	**6g**, R^2 = OCH_3, R^3 = *n*-Bu	60
10	X = NCH_3, R^1 = H, R^2 = OCH_3	**6h**, R^2 = OCH_3, R^3 = *sec*-Bu	50
11	X = NCH_3, R^1 = H, R^2 = OCH_3	**7c**, R^2 = OCH_3, R^3 = *n*-Bu, E = CH_2OCH_3	50
12	X = NCH_3, R^1 = H, R^2 = OCH_3	**7d**, R^2 = OCH_3, R^3 = *n*-Bu, E = $CH_2CHOHCH_2CH_3$	60

(1) Subramanian, R.; Johnson, F. *J. Org. Chem.* **1985**, *50*, 5430.
(2) These results will be the subject of a separate publication.
(3) To our knowledge only one example of the anionic cyclization of acetylenes is known. This involves the conversion of 1-bromo-8-(2-phenylacetylene)acenaphthene to 1-phenylacenaphthane by butyllithium. Kandil, S. A.; Dessy, K. E. *J. Am. Chem. Soc.* **1966**, *88*, 3027.
(4) Tanaka, K.; Shiraishi, S.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1978**, 3103.
(5) The driving force for the formation of the carbon–carbon σ bond at the expense of the acetylenic bond may be derived from (a) the energy of rehybridization (acetylene to ethylene), (b) the additional delocalization of the newly formed heterocyclic system, and (c) the stabilization of the final anion at the 2-position by the adjacent heteroatom, although the differeces in energy between anion **4b** and anion **5** may only be marginal. Dessy and co-workers have discussed the cyclization mentioned in ref 3 above in a similar context.

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2,2,2-Trifluoroethyl 2-bromophenyl thioether **3** [X = S, R^1 = Br, R^2 = H; bp 64–65 °C (0.05 mm)] was used as the starting compound in the sulfur series. It was synthesized in the same way as the oxygen analogue noted above, and on treatment with 4 equiv of an alkyl- or aryllithium (R^3Li) in ether, gave, after quenching, without event, the thianaphthene[5] **6** or **7** (X = S). The lower yields in the benzofuran and thianaphthene series are probably due to competitive nucleophilic attack of the lithium reagent on the intermediate acetylenes to displace[4,6] phenoxide or thiophenoxide, respectively.

In the nitrogen series we used *N*-(2,2,2-trifluoroethyl)-*N*-methyl-*m*-anisidine **3** (X = NCH_3, R^1 = H, R^2 = OCH_3) as a model compound. This nonvolatile oil was synthesized[7] by reduction of *N*-(trifluoroacetyl)-*N*-methyl-*m*-anisidine with diborane and on treatment with 4 equiv of an alkyllithium (R^3Li), followed by quenching with H^+ or E (Scheme II), was cleanly converted to the substituted indoles **6** or **7** (X = NCH_3, R^2 = OCH_3).

Table I not only indicates the scope of the reaction but also demonstrates the potential for heterocyclic ring formation by this new intramolecular carbanionic addition to acetylenes.

The following preparation of the substituted indole **7d** illustrates the general experimental procedure: To a solution of *N*-(2,2,2-trifluoroethyl)-*N*-methyl-*m*-anisidine **3** (0.219 g, 1 mmol) in dry THF, under an atmosphere of nitrogen at −78 °C, was added *n*-BuLi (2 mL; 4 equiv; 2 M in hexane). The reaction was warmed to room temperature gradually over 4–6 h; after the mixture was cooled to 0 °C, 0.2 mL of 1,2-epoxy butane was added, and the mixture was stirred for 1 h. Aqueous workup and isolation of the product by dichloromethane extraction, followed by silica gel chromatography (8:2 hexane/ethyl acetate) gave indole **7d** as a pale yellow solid (0.170 g; 60%; mp 94–95 °C).

Alternate routes to the intermediate acetylenic compounds related to **4**, which should permit greater flexibility in the substitution pattern, are being explored. Attempts to utilize this general methodology for the synthesis of other heterocyclic ring systems are in progress.

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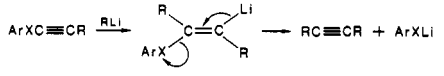
Registry No. **3** (X = O, R^1 = R^2 = H), 17351-95-0; **3** (X = S, R^1 = Br, R^2 = H), 105230-43-1; **3** (X = NMe, R^1 = H, R^2 = OMe), 60036-83-1; **6a**, 36724-27-3; **6b**, 105230-34-0; **6c**, 36724-25-1; **6d**, 105230-36-2; **6e**, 105230-37-3; **6f**, 14315-12-9; **6g**, 105230-39-5; **6h**, 105230-40-8; **7a**, 105230-35-1; **7b**, 105230-38-4; **7c**, 105230-41-9; **7d**, 105230-42-0; *N*-(trifluoroacetyl)-*N*-methyl-*m*-anisidine, 32368-27-7.

(6) It is known[4] for example that when 1-phenoxy-2-phenylacetylene is treated with phenyllithium only diphenyl acetylene is formed. A possible mechanism for the formation of these disubstituted acetylenic by products is noted below. This would be analogous to anionic additions



observed with 1-chloro-2-phenylacetylene (Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551) with the ArX group behaving as a pseudohalogen in our cases. However addition, at an earlier point during the dehalogenation process, cannot be ruled out.

(7) *N*-Methyl-*N*-(trifluoroacetyl)-*m*-anisidine (3.5 g, 1.5 mmol) and 30 mL of diborane (30 mmol, 1 M solution in THF) was heated under reflux under an atmosphere of nitrogen for 16 h. Normal workup followed by silica gel chromatography (9:1 hexane/ethyl acetate) gave 2.95 g (90%) of compound **3** (X = NCH_3, R^1 = H, R^2 = OCH_3).

(8) Satisfactory analytical and physical data were obtained for all new compounds reported.

(9) Ether rather than THF was used as the solvent in the cases of the thioethers.

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Allylic Stereocenter Directed Asymmetric Conjugate Addition. Enantioselective Synthesis of 3-Alkylsuccinaldehydic Acid Methyl Esters

Summary: Cuprate reagents add to ester **2** with excellent π-face selectivity (≥95:5) and furnish the title compounds in high enantiomeric excess after removal of the chiral auxiliary.

Sir: Asymmetric conjugate addition to α,β-unsaturated carbonyl compounds has been receiving considerable attention.[1,2] In particular the problem of additions to conjugated olefins bearing an allylic stereocenter has been considered from both a theoretical and experimental point of view.[2]

As a part of our study regarding π-face differentiation induced by a norephedrine-derived oxazolidine,[3] we examined conjugate addition to unsaturated ester **2**. We found that cuprate reagents add to **2** with excellent (≥95:5) diastereoselectivity to give in good yield esters **3a–f** (Scheme I, Table I).[4] Adducts **3** were in turn transformed into aldehydes **4a–d** of known absolute configuration[5,6] (Table II) by a two-step procedure (note *a*, Table II[7]) that allows the recovering of the intact chiral auxiliary.

Since both enantiomeric forms of norephedrine are commercially available this method allows the synthesis

(1) Tomioka, K.; Koga, K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 201. Posner, G. H. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 2, p 225. Lutomsky, K. A.; Meyers, A. I. *Asymmetric Synthesis*; Academic: New York, 1984; Vol. 3, p 213. Leading references: Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212. Soai, K.; Machida, H.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1985**, 469. Tomioka, K.; Sudani, M.; Shinmi, Y.; Koga, K. *Chem. Lett.* **1985**, 329. Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, 4967. Leyendecker, F.; Laucher, D. *Ibid.* **1983**, 3517. Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, 369. Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019. Heathcock, C. H.; Oare, D. A. *Ibid.* **1985**, *50*, 3022. Heathcock, C. H.; Norman, M. H., Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.

(2) (a) Trost, B. M.; Lynch, J.; Renaut, P. *Tetrahedron Lett.* **1985**, 6313 and references therein. (b) Roush, R. H.; Lesur, M. B. *Ibid.* **1983**, 2231 and references therein. (c) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. Heathcock, C. H.; Uehling, D. E. *J. Org. Chem.* **1986**, *51*, 279. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, 6015.

(3) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C.; DeMunari, S. *Tetrahedron Lett.* **1985**, 5459.

(4) Chiral oxazolidines derived from ephedrine have been used as 1,3-asymmetric inductors in cuprate additions to unactivated double bonds for the stereoselective synthesis of β-alkyl aldehydes with fairly good results: Hucke, M.; Auboult, J.; Pourcelot, G.; Berlan, J. *Tetrahedron Lett.* **1983**, 585. Mongeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1984**, *40*, 1803. Berlan, J.; Besace, J.; Stephan, E.; Cressan, P. *Tetrahedron Lett.* **1985**, 5765.

(5) Asymmetric synthesis of 3-alkylsuccinaldehydic acid methyl esters was described by Mukaiyama: Asami, M.; Mukayiama, T. *Chem. Lett.* **1979**, 569.

(6) **3e** and **3f** were reduced respectively to **3c** and **3d** (5% Rh–alumina, H_2), before removing the chiral auxiliary.

(7) Under the conditions here described **3e** underwent double bond migration to give the more stable α,β-unsaturated aldehyde.

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