A Versatile Synthetic Method for Preparing 1,2,3,5-Tetrasubstituted Pyrroles Using Isothiocyanates and 2-Alkynyl Ethers or 2-Alkynylamines as Building Units

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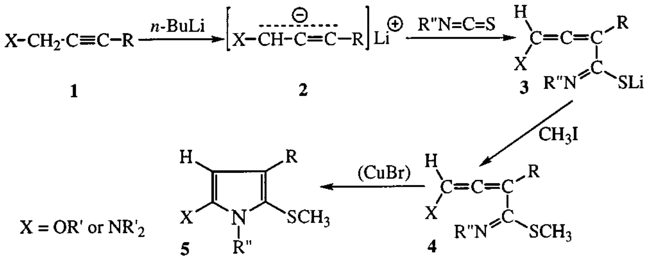
A fundamentally new approach for the construction of pyrrole rings is exemplified by highly efficient one-pot syntheses of 1,2,3,5-tetrasubstituted pyrroles starting from alkyl isothiocyanates and 2-alkynylamines or 2-alkynyl ethers.

The reactions of alkyl- and aryllithium compounds or the corresponding Grignard reagents with isocyanates and isothiocyanates have been utilized in the synthesis of carboxamides and thioamides.[1−3] In recent papers, we have shown by efficient syntheses of 1,2- and 2,3-dihydropyridines, 3- and 5-substituted 2-aminothiophenes, quinolines, and cyclobutanopyrrolines[4−8] that the combination of an *unsaturated* carbanion with an isothiocyanate offers interesting, hitherto unexplored synthetic possibilities.

We report herein a fundamentally new approach for the construction of the pyrrole ring, the crucial step being the regiospecific functionalization of lithiated 2-alkynylamines or the analogous ethers with alkyl isothiocyanates (for reviews on known pyrrole ring syntheses, see ref.[9−12]).



Scheme 1. One-pot procedure for 1,2,3,5-tetrasubstituted pyrroles

Addition of an alkyl isothiocyanate R″N=C=S to the lithium compounds **2** and subsequent *S*-methylation afforded azatrienes **4**. In some cases, **4** underwent spontaneous cyclization to the tetrasubstituted pyrroles **5** during workup, but generally catalytic amounts of copper(I) bromide appeared to be necessary for this purpose. In most cases, the yields of pyrroles **5** obtained in this one-pot procedure exceeded 65%. Metallation of the amines (**1**, X = NR′$_2$), which proceeded rather slowly with *n*BuLi, could be achieved more rapidly by using the Lochmann−Schlosser equimolar combination of *n*BuLi and *t*BuOK, with subsequent addition of anhydrous lithium bromide.

Our preliminary results, exemplified by the two procedures outlined here, indicate that the method has a broad scope. The starting compounds can be conveniently synthesized by standard methods described in laboratory manuals.[13−15] Some of the *ethers* **1** may even be prepared in situ from lithiated 1-alkynes and chloromethyl methyl ether.

Full details will be published in due course.

Experimental Section

5-(Diethylamino)-3-(diethylaminomethyl)-1-ethyl-2-(methylthio)-pyrrole (5: R = CH$_2$NEt$_2$; X = NEt$_2$; R″ = Et): To an efficiently stirred mixture of 0.07 mol of *t*BuOK and 0.05 mol of $Et_2NCH_2C{\equiv}CCH_2NEt_2$ in THF (50 mL), a solution of 0.07 mol of *n*BuLi in ca. 45 mL of hexane was added over a period of 2 min, with the temperature being maintained in the range −100 to −90°C. Following this addition, the cooling bath (liquid N$_2$) was removed and the temperature was allowed to rise to −40°C over 10 min (occasional cooling). Then, a solution of 6.5 g of anhydrous lithium bromide in THF (25 mL) was added at −70°C. After 1 min, the gelatinous suspension was cooled to −70°C once more and 0.05 mol of ethyl isothiocyanate was added in a single portion. The cooling bath was removed and the temperature was allowed to rise to −20°C, whereupon 11.5 g of methyl iodide was added. When the temperature of the mixture had reached +14°C, the flask was insulated with cotton wool and 1 g of finely powdered copper(I) bromide was added. The temperature of the slowly stirred mixture rose to ca. 37°C within 15 min. After a further 15 min, 100 mL of a concentrated aqueous solution of ammonia, containing 20 g of ammonium chloride, was added. After stirring for 10 min, the layers were allowed to separate and the aqueous layer was extracted twice with small portions of diethyl ether. The dried combined organic solutions (K$_2$CO$_3$) were filtered through a 5-cm layer of neutral Al$_2$O$_3$ in order to remove traces of copper compounds (which have been shown to induce decomposition during distillation). Concentration of the filtrate followed by distillation (b.p. ca. 100°C/0.5 Torr, n_D^{20} = 1.5128) gave the pyrrole (purity 96.5% by GLC) in 87% yield. − ^{1}H NMR (90 MHz, CCl$_4$): δ = 5.75 (s, 1 H), 4.05 (q, 2 H), 3.48 (s, 2 H), 2.90 (q, 4 H), 2.45 (q, 4 H), 2.15

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1434−193X/99/1010−2663 $ 17.50+.50/0

(s, 3 H), 1.27 (t, 3 H), 1.05 (dt, 12 H). − Exact mass: calcd. 297.2239; found 297.2310.

One-Pot Procedure for 3-(2-Furyl)-5-methoxy-1-methyl-2-(methylthio)pyrrole (5: R = 2-furyl; X = OMe; R′′ = Me): A solution of 0.05 mol of 2-furylacetylene in THF (50 mL) was cooled to −60°C. Then, *n*BuLi (0.05 mol) in hexane (35 mL) was injected, followed by 0.05 mol of chloromethyl methyl ether. The resulting mixture was warmed to 10°C, whereupon an exothermic reaction commenced, which led to a temperature increase of up to ca. 40°C. After a further 15 min at 40−45°C, the suspension was cooled to −100°C and 0.05 mol of *n*BuLi in hexane (35 mL) was added over a period of 5 min by means of a syringe, with the temperature being maintained between −100 and −90°C. Following this addition, the temperature of the dark-brown solution was allowed to rise to −60°C. It was then cooled to −100°C once more and a solution of 0.05 mol of methyl isothiocyanate in THF (10 mL) was added in a single portion. When the temperature had reached −30°C, 13 g of methyl iodide was added. The mixture was warmed to +10°C and the flask was insulated with cotton wool. Copper(I) bromide (1 g) was then added and the mixture was gently stirred. The temperature rose to over 30°C within half an hour. After warming for a further 30 min at ca. 30°C, the product (b.p. ca. 100°C/0.5 Torr, purity 99% by GLC) was isolated (ca. 63% yield) as described in the preceding procedure. − ^{1}H NMR (90 MHz, CCl_4): δ = 7.27 (m, 1 H), 6.75 (m, 1 H), 6.34 (m, 1 H), 5.58 (s, 1 H), 3.80 (s, 3 H), 3.48 (s, 3 H), 2.15 (s, 3 H). − Exact mass: calcd. 223.0667; found 223.0653. − *Note:* The in-situ prepared 3-(2-furyl)-propargyl methyl ether can also be synthesized from 2-bromofuran and methyl propargyl ether in triethylamine in the presence of $Pd(PPh_3)_4$ and CuBr.[15]

[1] B. J. Wakefield, *Organolithium Methods*, Academic Press, London, **1988**, p. 96, 102.

[2] K. A. Petrov, L. N. Andreev, *Usp. Khim.* **1969**, *38*, 41−71.

[3] M. S. Kharash, O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, New York, **1954**, chapter XIX.

[4] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, V. Yu. Vvedensky, B. A. Trofimov, *Tetrahedron Lett.* **1998**, *39*, 1995−1996.

[5] N. A. Nedolya, L. Brandsma, B. A. Trofimov, *Dokl. Akad. Nauk.* **1996**, *350*, 68−69; *Khim. Geterotsikl. Soedin* **1996**, 917−918; *Izv. Akad. Nauk., Ser. Khim.* **1996**, 2813−2814; *Russ. Chem. Bull.* **1996**, *45*, 2670−2671.

[6] O. A. Tarasova, L. V. Klyba, V. Yu. Vvedensky, N. A. Nedolya, H. D. Verkruijsse, B. A. Trofimov, L. Brandsma, *Eur. J. Org. Chem.* **1998**, 253−256.

[7] L. Brandsma, N. A. Nedolya, O. A. Tarasova, L. V. Klyba, L. M. Sinegovskaya, B. A. Trofimov, *Dokl. Akad. Nauk.* **1997**, *357*, 350−351.

[8] L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, N. L. Owen, Du Li, B. A. Trofimov, *Tetrahedron Lett.* **1997**, *38*, 6905−6908.

[9] A. Gossauer, *Die Chemie der Pyrrole*, Springer-Verlag, Heidelberg, **1974**.

[10] B. A. Trofimov, A. I. Mikhaleva, *N-Vinylpirroly*, Nauka, Novosibirsk, **1984**.

[11] R. A. Jones (Ed.), *Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles*, part II in the series *The Chemistry of Heterocyclic Compounds*, John Wiley, Chichester, **1992**.

[12] J. M. Patterson, *Synthesis* **1976**, 281−304.

[13] L. Brandsma, *Preparative Acetylenic Chemistry*, 2nd ed., Elsevier, Amsterdam, **1988**.

[14] L. Brandsma, H. D. Verkruijsse, *Synthesis of Acetylenes, Allenes and Cumulenes, A Laboratory Manual*, Elsevier, Amsterdam, **1981**.

[15] L. Brandsma, S. F. Vasilevsky, H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer-Verlag, Heidelberg, **1998**.

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