An Expedient Synthesis of Pyrrole Derivatives by Reaction of Lithiated Methoxyallenes with Imines

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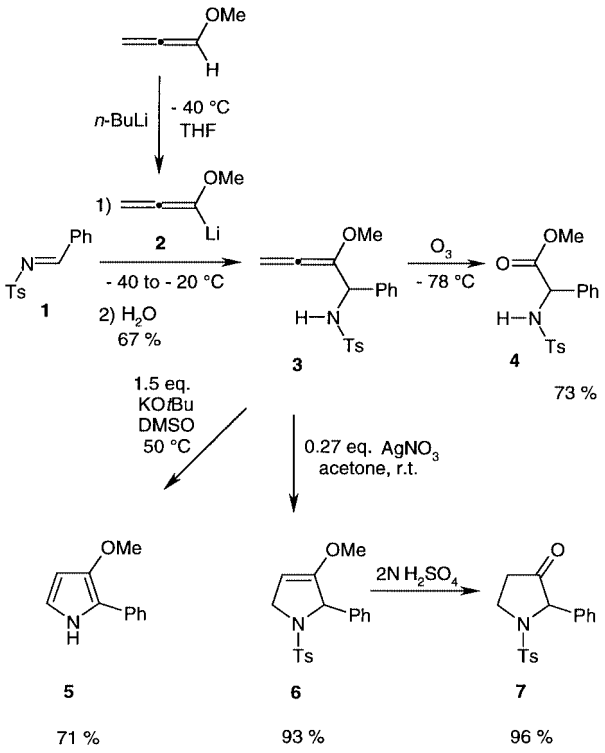
Abstract: Addition of lithiated methoxyallene **2** to imines provided the expected allenyl amines in good yield. These could be cyclized with base or with silver nitrate to a variety of 2,5-dihydropyrrole derivatives. Selected examples describe their conversion to pyrrolidin-3-ones or 3-methoxypyrroles. Most importantly, this [3+2] cyclization method could also be applied to the synthesis of 2,5-disubstituted derivatives such as **26**-**28** and also to the preparation of the enantiopure compound **23**.

Key words: methoxyallene, imine, allenyl amine, 2,5-dihydropyrrole, pyrrolidin-3-one, 3-methoxypyrrole

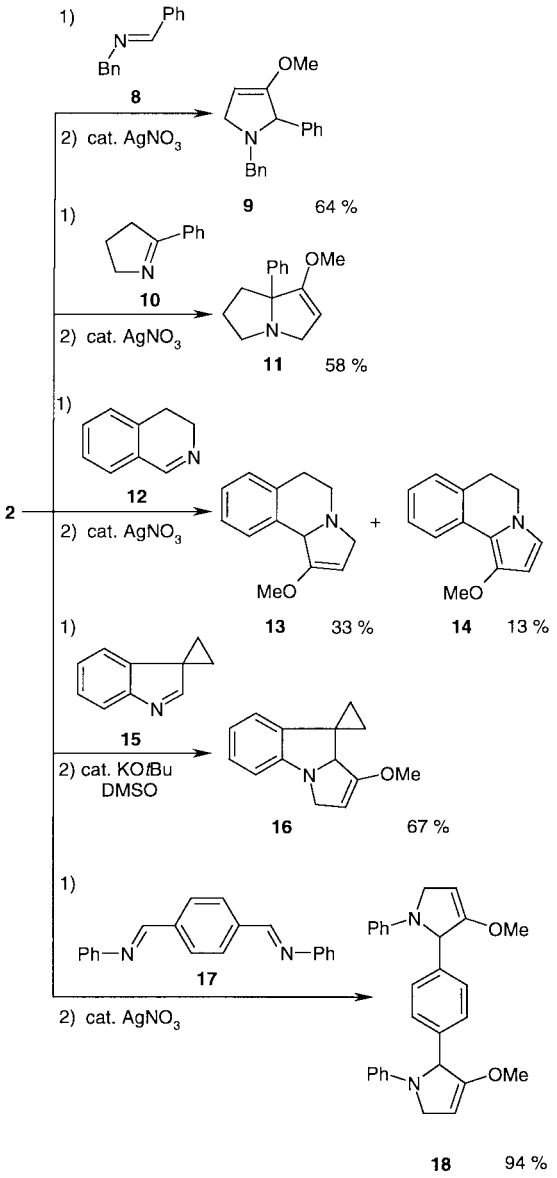
Syntheses of pyrrole derivatives are of great importance due to their presence in numerous biologically active compounds.[2] Therefore, many routes leading to this class of heterocycles have been developed.[3] In addition, certain electron-rich pyrrole derivatives are of interest because of their redox behaviour and their ability to provide polypyrroles.[4] Lithiated methoxyallene **2** is an extremely valuable building block for the synthesis of oxygen and nitrogen heterocycles.[5] With carbonyl compounds it provides furan derivatives after cyclization,[6] whereas its reaction with nitrones leads to 1,2-oxazines.[7] Surprisingly, no additions to simple imines have been reported,[8] which should furnish pyrrole derivatives. A recent publication describing reactions of **2** with SAMP-hydrazones providing enantiopure 3-methoxy-2,5-dihydropyrrole derivatives[9] prompts us to report our results with various imines.[10]



Scheme 1

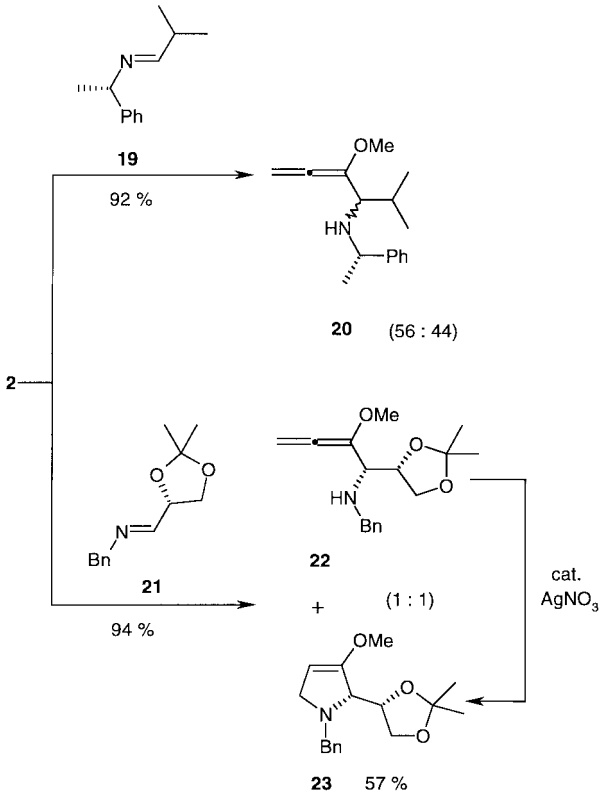
Lithiated methoxyallene **2** was generated by the standard procedure employing *n*-butyllithium at -40 °C, and after addition of *N*-tosylimine **1**[11] followed by aqueous workup and purification the primary adduct **3** was obtained in 67% yield (Scheme 1). This intermediate could be hydrolyzed with acid to afford an α,ß-unsaturated ketone[10] or, more interestingly, converted into α-amino ester **4** by ozonolysis.[12]

In analogy to the behaviour of the carbonyl adducts[6] cyclization of **3** employing 0.15 equivalents of potassium *tert*-butoxide in DMSO furnished the desired pyrrole derivative **6** in 84% yield. Since an excess of base converts **6** into **5**, the isomerization **3**→**6** is better performed by using of 0.27 equivalents of silver nitrate in acetone[13] which gave a yield of 93%.[14] Cyclization of **3** and elimination of toluene sulfinate from intermediate **6** proceeded by use of 1.5 equivalents of KO*t*Bu and furnished 3-methoxy-2-phenylpyrrole (**5**) in 71% yield. This compound was also formed by heating the primarily obtained lithium salt of **3** in DMSO. An obvious subsequent transformation of 2,5-dihydropyrrole derivative **6** is the hydrolysis of its enol ether moiety; treatment of **6** with 2N aqueous sulfuric acid provided pyrrolidinone **7** in 96% yield. Analogous experiments were successfully performed with *N*-tosyl imines derived from pivalaldehyde and cinnamyl aldehyde. Having established that highly reactive imines such as **1** behave similarly to carbonyl compounds, we studied less reactive *N*-aryl and *N*-alkyl imines. Scheme 2 presents selected examples of the additions of **2** to readily available imines **8**, **10**, **12**, **15**, and **17**. Cyclization either with silver nitrate or under basic conditions cleanly afforded the expected pyrrole derivatives **9**, **11**, **16** and **18** in good to excellent overall yields, whereas tricyclic compound **13** was accompanied by the dehydrogenated product **14**. Of particular interest is the smooth formation of double adducts such as **18** (1:1 mixture of diastereomers) since compounds of this type may be valuable components of supramolecular systems.



Scheme 2

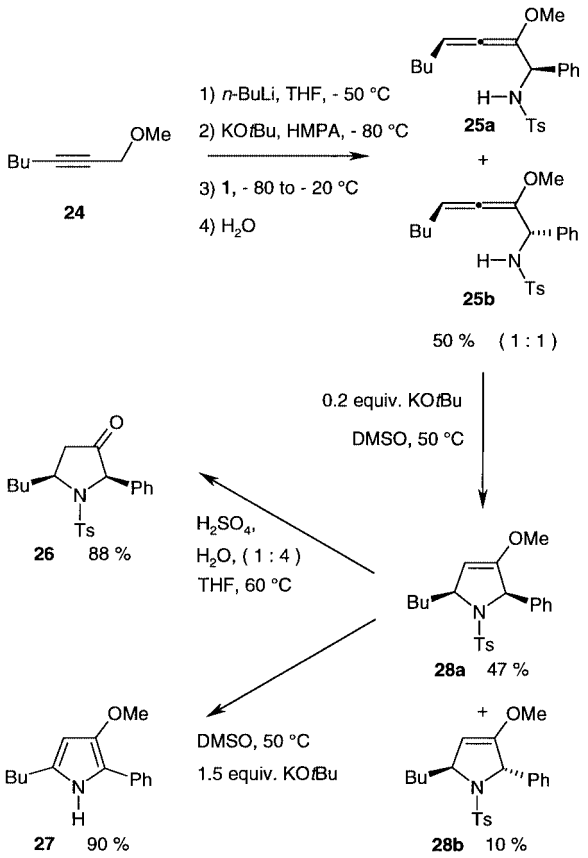
We also started to prepare enantiopure compounds following this approach (Scheme 3). A phenethyl group at the imine nitrogen present in **19** induced almost no diastereomeric excess as demonstrated by formation of **20** (ratio of diastereomers 56:44). However, *(R)*-glyceraldehyde derived imine **21**[15] reacted with lithiated methoxyallene **2** with excellent diastereofacial selectivity. Only *syn* compounds **22** and **23** were formed as a 1:1 mixture.[16] The cyclization was completed with silver nitrate to provide enantiopure 2,5-dihydropyrrole derivative **23** in 57% yield. The *syn*-configuration was anticipated according to literature precedence[17] and proven by comparison with a compound obtained by an independent route;[18] in addition, an X-ray analysis of the analog *N*-phenyl derivative unequivocally demonstrated the relative configuration of these compounds.



Scheme 3

Initial experiments were devoted to the preparation of 5-alkyl substituted pyrrole derivatives using this route. Thus, 1-methoxy-1,2-heptadiene could successfully be employed for this purpose.[19] However, it turned out that 1-methoxy-2-heptyne (**24**)[20] allows an even more efficient approach (Scheme 4). Its deprotonation and treatment with KO*t*Bu/HMPA followed by addition of *N*-tosyl imine **1** provided allene **25** as a mixture of diastereomers (1:1) in 50% yield. The base catalyzed cyclization of **25a**/**25b** afforded a mixture of 2,5-dihydropyrrole derivatives **28a** (47%) and **28b** (10%); a small amount of **25b** was re-isolated.[21] This experiment demonstrates that pyrrole formation is not hampered by the terminal substituent at the methoxyallene moiety although it proceeds more slowly.

Diastereomer **28a** was smoothly transformed into 2,5-*cis*-substituted pyrrolidin-3-one **26** by acid treatment, or into 5-butyl-3-methoxy-2-phenylpyrrole (**27**) by base promoted elimination. These high yielding processes demonstrate that the cyclizations of allenyl amines[22] as described in this letter should allow the preparation of a variety of highly substituted and functionalized pyrrole derivatives. First examples of this [3+2] cyclization method also reveal that control of relative and absolute configuration is possible.



Scheme 4

Acknowledgement

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References and Notes

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(2) For recent examples see: K. Ishii, H. Ohno, Y. Takemoto, T. Ibuka, *Synlett* **1999**, 228-230 and references cited.

(3) Reviews: a) R. J. Sundberg in *Comprehensive Heterocyclic Chemistry* (Eds. A. R. Katritzky, C. W. Rees), p. 313-376, Pergamon, Oxford 1984. b) G. P. Beau in *Pyrroles* (Ed. R. A. Jones), *The Chemistry of Heterocyclic Compounds* (Eds. E. C. Taylor, A. Weissberger), p. 105-294, Wiley: New York 1990. c) R. J. Sundberg in *Comprehensive Heterocyclic Chemistry II* (Eds. A. R. Katritzky, C. W. Rees, E. F. V. Scriven), p. 119-206, Pergamon: Oxford 1996. d) S. E. Korostova, A. I. Mikhaleva, A. M. Vasil'tsov, B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)* **1998**, *34*, 911-948. e) S. E. Korostova, A. I. Mikhaleva, A. M. Vasil'tsov, B. A. Trofimov, *Russ. J. Org. Chem. (Engl. Transl.)* **1998**, *34*, 1691-1714. f) For a recent synthesis employing electron-deficient allene derivatives and imines: Z. Xu, X. Lu, *J. Org. Chem.* **1998**, *63*, 5031-5041.

(4) a) A. Merz, T. Meyer, *Synthesis* **1999**, 94-99. b) A. Merz, J. Kronberger, L. Dunsch, A. Neudeck, A. Petr, L. Parkanyi, *Angew. Chem.* **1999**, *111*, 1533-1538; *Angew. Chem. Int. Ed.* **1999**, *38*, 1442-1446 and references cited.

(5) For a recent review see: H.-U. Reissig, S. Hormuth, W. Schade, M. Okala Amombo, T. Watanabe, R. Pulz, A. Hausherr, R. Zimmer, *J. Heterocyclic Chem.* **2000**, in press. For general reviews on the reactivity of alkoxyallenes see: a) R. Zimmer, *Synthesis* **1993**, 165-178. b) R. Zimmer, F. A. Khan, *J. Prakt. Chem.* **1996**, *338*, 92-94.

(6) Initial work: a) S. Hoff, L. Brandsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1179-1184. b) S. Hoff, L. Brandsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609-619. For applications to asymmetric syntheses: c) S. Hormuth, H.-U. Reissig, *J. Org. Chem.* **1994**, *59*, 67-73. d) S. Hormuth, W. Schade, H.-U. Reissig, *Liebigs Ann.* **1996**, 2001-2006. e) S. Hormuth, H.-U. Reissig, D. Dorsch, *Angew. Chem.* **1993**, *105*, 1513-1514; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1449-1450.

(7) W. Schade, H.-U. Reissig, *Synlett* **1999**, 632-634.

(8) a) N. A. Nedolya, L. Brandsma, O. A. Tarasova, H. D. Verkruijsse, B. A. Trofimov, *Tetrahedron Lett.* **1998**, *39*, 2409-2410. b) L. Brandsma, V. Yu. Vvedensky, N. A. Nedolya, O. A. Tarasova, B. A. Trofimov, *Tetrahedron Lett.* **1998**, *39*, 2433-2436.

(9) V. Breuil-Desvergnes, P. Compain, J.-M. Vatéle, J. Goré, *Tetrahedron Lett.* **1999**, *40*, 5009-5012.

(10) M. Okala Amombo, Diplomarbeit, Technische Universität Dresden 1997.

(11) a) R. Albrecht, G. Kresze, B. Mlakar, *Chem. Ber.* **1964**, *97*, 483-489. b) B. M. Trost, C. Marrs, *J. Org. Chem.* **1991**, *56*, 6468-6470.

(12) For a related approach see: M. Braun, K. Opdenbusch, *Liebigs Ann.* **1997**, 141-145.

(13) J. A. Marshall, G. S. Bartley, *J. Org. Chem.* **1994**, *59*, 7169-7171. Also see: A. Claesson, K. Sahlberg, K. Luthman, *Acta Chem. Scand.* **1979**, *B33*, 303.

(14) Typical procedure, **1+2→3→6**: Lithiated methoxyallene **2** was generated under an atmosphere of dry argon by treating a solution of 687 mg (9.80 mmol) methoxyallene in 20 ml of THF at -40 °C with 4.00 ml (8.82 mmol) of *n*-BuLi (2.2 M in hexane). After 5 min a solution of 1.70 g (6.54 mmol) of **1** in 7 ml of THF was added over a period of 5 min, the mixture was stirred for 2 h at -40 to -20 °C and quenched with 20 ml of H_2O. Warming to room temperature was followed by extraction with diethyl ether (3 x 20 ml) and drying of the combined extracts (Na_2SO_4). Removal of the solvent in vacuo yielded 2.15 g (99%) of crude **3** as a brown solid, which was purified by washing with diethyl ether. Compound **3** was obtained as a yellow solid (1.44 g, 67%, m. p. 100-101 °C). For analytical data see ref.[10]
Cyclization of **3**: To 300 mg (0.91 mmol) of allene **3** in 7 ml of acetone was added 42 mg (0.25 mmol) of $AgNO_3$, and the resulting mixture was stirred in the dark under argon at room temperature for 3 h. The mixture was filtered through a pad of celite with ethyl acetate. The filtrate was concentrated to afford pure 2,5-dihydropyrrole **6** as a yellow solid (280 mg, 93%, m. p. 155-157 °C).
Analytical data of **6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.51 (d, *J* = 8.2 Hz, 2 H, Tos), 7.26 (s, 5 H, Ph), 7.18 (d, *J* = 8.2 Hz, 2 H, Tos), 5.25-5.22 (m, 1 H, 4-H), 4.57 (q, *J* = 1.6 Hz, 1 H, 2-H), 4.30-4.25 (m, 2 H, 5-H), 3.50 (s, 3 H, OMe), 2.38 (s, 3 H, Me).
^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 156.6 (s, C-3), 143.1, 139.4, 135.4 (3 s, i-C), 129.4, 128.3, 128.0, 127.6, 127.3 (5 d, Ar, Ph), 89.0 (d, C-4), 67.3 (d, C-2), 57.3 (q, OMe), 52.3 (t, C-5), 21.5 (q, Me). - IR (KBr): ν = 3100-3000 cm^{-1} (= C-H), 3000-2840 (C-H), 1670-1600 (C=C), 1350-1310, 1160-1120

(SO_2), 1250 (C-O). - $C_{18}H_{19}NO_3S$ (329.4) Calcd. C 65.63, H 5.81, N 4.25, S 9.73; found C 65.73, H 5.89, N 4.27, S 9.48.
(15) J. Yoshimura, Y. Ohgo, T. Sato, *J. Am. Chem. Soc.* **1964**, *86*, 3858-3862. Also see: L. Battistini, F. Zanardi, G. Rassu, P. Spanu, G. Pelosi, G. G. Fava, M. B. Ferrari, G. Casiraghi, *Tetrahedron: Asymmetry* **1997**, *8*, 2975-2987.
(16) Primary adducts with an *N*-alkyl substituent such as **22** seem to undergo faster cyclization to 2,5-dihydropyrrole derivatives.
(17) For additions of organometallic reagents to this imine see: ref. 15. For general reviews on stereoselective additions to imines see: a) N. Risch, M. Arend in *Stereoselective Synthesis of Organic Compounds/Methods of Organic Chemistry (Houben-Weyl)*, 4th Ed., *Vol. E21b* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart 1995, p. 1833-2010. b) D. Enders, U. Reinhold, *Tetrahedron: Asymmetry* **1997**, *8*, 1895-1946. c) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407-1438.
(18) A 1,2-oxazine with *syn*-configuration could be converted into **23**. T. Watanabe, unpublished results, Technische Universität Dresden 1998.
(19) A. Hausherr, unpublished results, Technische Universität Dresden 1999.
(20) Performed in analogy to L. Brandsma, H. D. Verkruijsse, W. Verboom, P. E. Van Riju, *J. Organomet. Chem.* **1982**, *232*, C1-C4.
(21) The cyclization of **25** is probably stereospecific. Thus, diastereomer **25a** provides only *cis*-substituted **28a** whereas the slower reacting **25b** gives *trans*-isomer **28b**. Details will be presented in a full paper.
(22) For related 5-*endo*-trig cyclizations of allenyl amines furnishing 2,5-dihydropyrrole derivatives see: a) J. S. Prasad, L. S. Liebeskind, *Tetrahedron Lett.* **1988**, *29*, 4253-4256. b) J. S. Prasad, L. S. Liebeskind, *Tetrahedron Lett.* **1988**, *29*, 4257-4260. c) K. Schierle, R. Vahle, E. Steckhan, *Eur. J. Org. Chem.* **1998**, 509-514. d) H. Ohno, A. Toda, Y. Miwa, T. Taga, E. Osawa, Y. Yamaoka, N. Fujii, T. Ibuka, *J. Org. Chem.* **1999**, *64*, 2992-2993.

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