Pergamon

Tetrahedron Letters, Vol. 36, No. 44, pp. 8007-8010, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01717-8

New Efficient and Flexible Synthesis of Polysubstituted Pyrroles

Dieter Enders*, Sin-Ho Han[1] and Ralf Maaßen

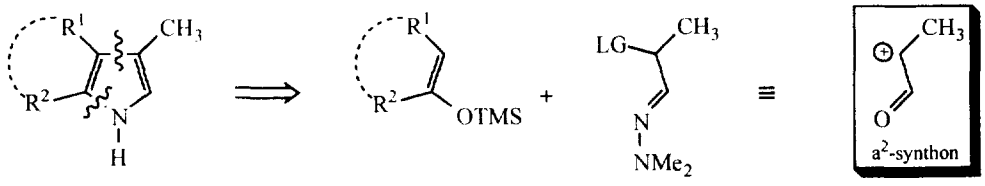
Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule
Professor-Pirlet-Straße 1, D-52074 Aachen, Germany

Abstract: The Lewis acid mediated reaction of readily available 2-acetoxypropanal-*N*,*N*-dimethylhydrazone **1** with various open chain and cyclic silyl enol ethers **2** leads directly or *via* 4-oxoaldehyde-*N*,*N*-dimethylhydrazones **3** to *N*-(dimethylamino)-pyrroles **4**. The subsequent reductive N-N bond cleavage provides an efficient and flexible method for the preparation of alkyl-aryl-di- and trisubstituted pyrroles **5**.

The pyrrole ring is the characteristic subunit of many natural products such as bile pigments, porphyrin based compounds and related macrocycles[2]. The synthesis of these compounds therefore affords elaborate methods for the construction of pyrrole rings with variable substitution patterns. Since the first pyrrole syntheses[3] at the end of the last century many efforts were made to develop new methodologies for the formation of alkyl-aryl-substituted[4a-i] and side chain functionalized[4f,h,j-o] pyrroles.

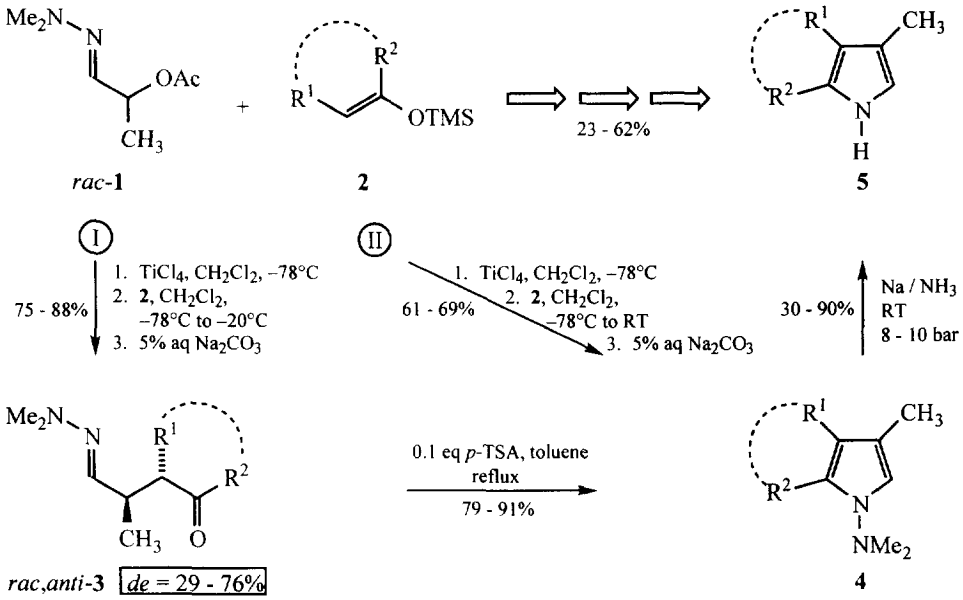
Among the numerous methods for the synthesis of pyrrole ring systems the [3+2] cyclization of a C_2N and a C_2 fragment, thus forming the N-C(2) and C(3)-C(4) bonds, is probably one of the most important variants. The best known and most variable representative of this type of reaction is the Knorr synthesis[2,3a], a widely used method for the preparation of pyrrole based natural compounds. Recently, alternative pyrrole syntheses based on the C(3)-C(4) bond formation have been reported by Ahlbrecht et al.[4b], Chelucci et al.[4c], Neier et al.[4h] and Nakanishi, Otsuji et al.[4i].

Our own retrosynthetic analysis of the pyrrole system **A** traced us back to simple silyl enol ethers **B** as the C_2 fragment with normal d^2-reactivity and the dimethylhydrazone **C** as the C_2N unit bearing a leaving group (LG) in α-position. The latter should serve as a synthetic equivalent of the a^2-synthon **D** (Umpolung of classical d^2-reactivity)[5].



A **B** **C** **D**

We now wish to report a new efficient and flexible synthesis of polysubstituted pyrroles from 2-acetoxypropanal-*N*,*N*-dimethylhydrazone[6] (*rac*-**1**) and various open chain and cyclic silyl enol ethers **2**. Key step of the new protocol is the Lewis acid mediated nucleophilic attack of the silyl enol ethers at the position 2 of the hydrazone *rac*-**1**. Thus *N*-(dimethylamino)-pyrroles **4** can be obtained either in two steps *via* 4-oxoaldehyde-*N*,*N*-dimethylhydrazones **3** (reaction pathway I) or directly in an one pot synthesis (reaction pathway II). Finally, subsequent reductive N-N bond cleavage of the amino pyrroles **4** leads to di- and trisubstituted pyrroles **5** in good overall yields.



As is shown in the scheme, the dimethylhydrazone *rac*-**1** was treated with titanium tetrachloride in CH_2Cl_2 at –78°C resulting in a 1:1-complex, which may be isolated as a yellow solid, followed by silyl enol ethers **2** to form 4-oxoaldehyde-*N*,*N*-dimethylhydrazones **3**. These could be obtained by allowing the reaction mixture to warm to –20°C over 3h and quenching with 5% aqueous sodium carbonate. After extraction of the aqueous layer with CH_2Cl_2 the combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. The crude products were purified by column chromatography (silica gel, petrol ether : ether = 2:1) to afford pure **3** in good to excellent yields and as anti-diastereomers in excess (de = 29-76%) based on careful ^{1}H-NMR investigation (table 1). The *de*-values were determined by ^{1}H-, ^{13}C-NMR spectroscopy and gas chromatography.

The 4-oxoaldehyde-*N*,*N*-dimethylhydrazones **3** could easily be converted to the *N*-(dimethylamino)-pyrroles **4** by heating to reflux in toluene in the presence of 0.1 eq toluenesulfonic acid (*p*-TSA) with azeotropic removal of water (reaction pathway I).

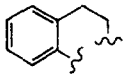
Table 1. 4-Oxoaldehyde-*N*,*N*-dimethylhydrazones **3**

3	R^1	R^2	yield [%]	*de*[a] [%]
a	H	CH_3	88	
b	CH_3	C_2H_5	81	62 (60)
c	H	$C(CH_3)_3$	86	
d	H	C_6H_5	82	
e	CH_3	C_6H_5	86	76 (77)
f		$-(CH_2)_3-$	75	29 (21)
g		$-(CH_2)_4-$	80	29 (30)

[a] Determined by ^{1}H-NMR spectroscopy; in brackets: determined by gas chromatography

Alternatively, the amino pyrroles **4** could be obtained in an one pot reaction by adding the silyl enol ether **2** dropwise to a suspension of the titanium complex of *rac*-**1** in CH_2Cl_2 at –78°C. The mixture was then slowly warmed to room temperature and stirred for 1 - 5 d (reaction pathway II). After quenching with 5% aqueous sodium carbonate the aqueous layer was extracted with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Pure *N*-(dimethylamino)-pyrroles **4** were obtained by column chromatography (silica gel, petrol ether : ether = 4:1; table 2).

Table 2. *N*-(Dimethylamino)-pyrroles **4** and Alkyl-Aryl-Substituted Pyrroles **5**

			N-(dimethylamino)-pyrroles **4**		pyrroles **5**	
entry	R^1	R^2	pathway	overall yield [%]	yield [%]	overall yield [%]
a	H	CH_3	I	70	32[a]	
b	CH_3	C_2H_5	I	66		
c	H	$C(CH_3)_3$	I	78	30	23
d	H	C_6H_5	I	71	85	60
e	CH_3	C_6H_5	I	76	82	62
f		$-(CH_2)_3-$	I	62	90	56
g		$-(CH_2)_4-$	II	68		
h		$-(CH_2)_5-$	II	61	82	50
i			II	69	89	61

[a] Yield of the crude product; the alkyl-substituted pyrroles are known to be sensitive compounds.

For the N-N bond cleavage of the *N*-(dimethylamino)-pyrroles **4** the reduction with sodium in liquid ammonia at room temperature under 8 - 10 bar pressure turned out to be the most efficient method. After dropwise addition of **4** in absolute THF to a solution of sodium (10 eq) in liquid ammonia at –50°C in an autoclave the temperature was allowed to rise to room temperature (8 - 10 bar vapour pressure) and the mixture was stirred for 3h at ambient temperature. The flask was then cooled to –50°C and methanol was added to quench excess sodium. The cooling bath was removed and the ammonia evaporated. After addition of water the reaction mixture was extracted with ether, the organic layers were dried over Na_2SO_4 and the solvent

was evaporated. Column chromatography (Al_2O_3, petrol ether : ether = 4:1) afforded pure pyrrole **5** in good yields (table 2).

In conclusion, the a^2-Umpolung reaction of 2-acetoxypropanal-*N,N*-dimethylhydrazone with silyl enol ethers in the presence of titanium tetrachloride followed by reductive N-N bond cleavage of the resulting *N*-(dimethylamino)-pyrroles provides an efficient and flexible method for the regioselective synthesis of alkyl-aryl-substituted pyrroles. Especially aryl-substituted and ring-fused pyrroles are obtained in good overall yields. The optimisation of the stereoselectivity of the novel C-C bond formation at the stage of the hydrazones **3**, which are potential precursors of 4-oxoaldehydes and 4-oxonitriles, is currently being investigated in our laboratories.

Acknowledgements. This work was supported by the Volkswagen-Stiftung, the European Union (Human Capital and Mobility Network: Metal Mediated and Catalyzed Organic Synthesis) and by the Fonds der Chemischen Industrie. We thank Wacker Chemie, BASF AG, Bayer AG and Hoechst AG for their donation of chemicals.

REFERENCES AND NOTES

1. Part of the dissertation of S.-H. Han, Technical University of Aachen, 1990.
2. (a) Gossauer, A. *Die Chemie der Pyrrole*; Springer-Verlag: Berlin, 1974; pp. 189ff, and references cited therein. (b) Sundberg, R. J.; Smith, K. M. in *Comprehensive Heterocyclic Chemistry*, Vol. 4, Part 3; Bird, C. W.; Cheeseman, G. W. H. Eds.; Pergamon Press: Oxford, 1984; pp. 313-442.
3. (a) Knorr, L. *Chem. Ber.* **1884**, *17*, 1635-1642. (b) Hantzsch, A. *Chem. Ber.* **1890**, *23*, 1474-1476. (c) Feist, F. *Chem. Ber.* **1902**, *35*, 1537-1544.
4. For some recent examples see: (a) Engel, N.; Steglich, W. *Angew. Chem.* **1978**, *90*, 719-720; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 676. (b) Ahlbrecht, H.; von Daacke, A. *Synthesis* **1984**, 610-614. (c) Chelucci, G.; Marchetti, M. *J. Heterocyclic Chem.* **1988**, *25*, 1135-1137. (d) Miyashita, M.; Elshtaiwi Awen, B. Z.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1989**, 841-842. (e) Baccolini, G. *J. Chem. Soc. Perkin Trans. I* **1989**, 1053-1056. (f) Sobenina, L. N.; Mikhaleva, A. I.; Trofimov, B. A. *Russ. Chem. Rev.* **1989**, *58*, 163-180. (g) Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193-1232. (h) Bertschy, H.; Meunier, A.; Neier, R. *Angew. Chem.* **1990**, *102*, 828-830; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 777. (i) Nakanishi, S.; Otsuji, Y.; Itoh, K.; Hayashi, N. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3595-3600. (j) Montforts, F.-P.; Schwartz, U. M.; Maib, P.; Mai, G. *Liebigs Ann. Chem.* **1990**, 1037-1043. (k) Alberola, A.; Andrés, J. M.; Gonzáles, A.; Pedrosa, R.; Vicente, M. *Heterocycles* **1990**, *31*, 1049-1058. (l) Hombrecher, H. K.; Horter, G. *Synthesis* **1990**, 389-391. (m) Jacobi, P. A., Cai, G. *Tetrahedron Lett.* **1991**, *32*, 1765-1768. (n) Baciocchi, E.; Muraglia, E.; Sleiter, G. *J. Org. Chem.* **1992**, *57*, 2486-2490. (o) Ueda, T.; Uchida, C.; Nagai, S.-I.; Sakakibara, J. *J. Chem. Soc. Perkin Trans. I* **1994**, 2201-2202.
5. (a) Seebach, D. *Angew. Chem.* **1979**, *91*, 259-278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239. (b) Hase, T. A.; Koskimies, J. K. in *Umpoled Synthons*; Hase, T. A. Ed.; John Wiley & Sons, Inc.: New York, 1987; pp. 145-172.
6. 2-Acetoxypropanal-*N,N*-dimethylhydrazone (*rac*-**1**) can easily be obtained by adding 2-acetoxypropanal to a solution of *N,N*-dimethylhydrazine in ether in the presence of $MgSO_4$ at 0°C. After stirring at room temperature for 90 min the reaction mixture is filtered and the solvent is evaporated. The product is purified by distillation under reduced pressure (bp = 38°C / 0,05 Torr; 90% yield).

(*Received in Germany* 30 *August* 1995; *accepted* 8 *September* 1995)