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Application of Iminium Salts in the Synthesis of Fused Pyridines. Introduction of Substituents Using Ternary Iminium Perchlorates

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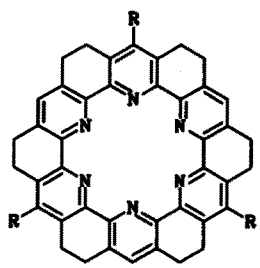
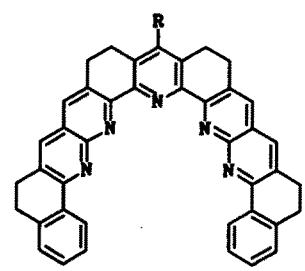
Key Words: Ternary iminium salts; Mannich reaction; alkyl and aryl substituted quino[1,x]phenanthrolines.

Abstract: Ternary iminium perchlorates are used as synthetic equivalents for aliphatic and aromatic aldehydes in a complex one pot reaction, providing an easy access to terpyridines with peripheral substituents. According to the proposed reaction mechanism this is the first example of an aminoalkylation of a ketone using this type of iminium salts. Surprisingly, the reaction produces "S-shaped" and "U-shaped" isomers. The distribution of isomeric products seems to be strongly influenced by electronic and/or steric properties of the substituent in the native iminium compound.



1a: R=H
1b: R=n-Butyl



2a: R=H
2b: R=CO_2Et

Fig. 1

Fused pyridines are very useful substructures in the design of supramolecular compounds, because of the donor function of the pyridine nitrogen.[1] Up to now, the synthesis of suitable polypyridine moieties is the limiting step in long synthetic sequences. Moreover, the larger molecules, such as the torands **1**,[2,3] or some polyaza cavities, e.g. **2**,[1a,4] exhibit only a poor solubility without peripheral substituents. According to the annelation pattern of these examples, the introduction of solubility improving carbon

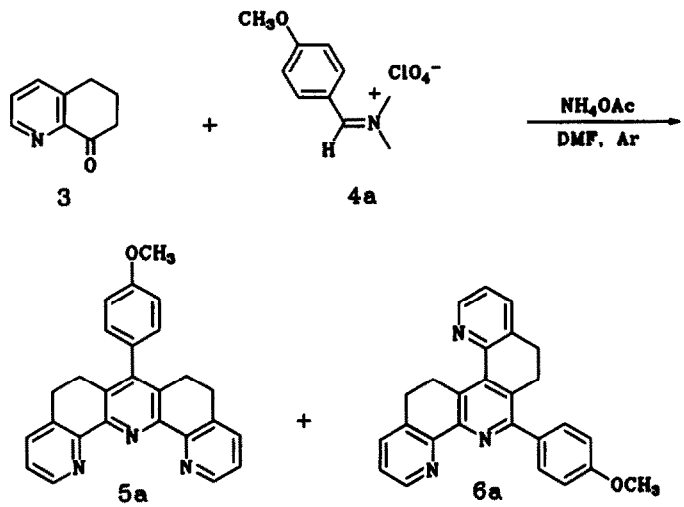
fragments into the central pyridine nucleus can only take place in the 4-position. In this paper, we present a convenient synthesis of substituted polypyridines, which show good solubilities in organic solvents or in water.

A simple synthetic approach for the construction of a central 4-aryl substituted pyridine unit was described by Thummel et al.[5] This method is based on a modified aldol condensation of the enamine of 6,7-dihydro-5*H*-quinolinone **3** with an aromatic aldehyde followed by Michael addition of a second enamine moiety to the arylidene ketone intermediate. The resulting 1,5-diketone precursor is condensed with ammonium acetate in a second reaction step.

Unfortunately, this procedure did not succeed for aliphatic aldehydes. Due to the ease of its enolization, side reactions might occur. Keeping the principal idea of this synthesis in mind, the problems should be overcome by replacement of the aldehyde with a suitable electrophilic synthetic equivalent.

In the course of our investigations into the Mannich reaction, we have recently developed a novel synthetic route for the preparation of unsubstituted, fused bi- and terpyridines, using Mannich bases or simply methylene iminium salts as building blocks.[6] Consequently, we describe here the results of the adaption of one of these procedures, using **ternary iminium perchlorates** as synthetic equivalents for both aliphatic and aromatic aldehydes.

The synthesis of ternary iminium salts **4** is easily achieved by condensation of dimethylamine perchlorate (or other suitable secondary amine perchlorates) and the appropriate aldehyde following the procedure of Leonard.[7] Most of these compounds are unusually stable against moisture compared with the better known methylene iminium salts.



Scheme 1

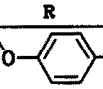
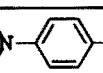
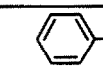
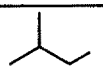
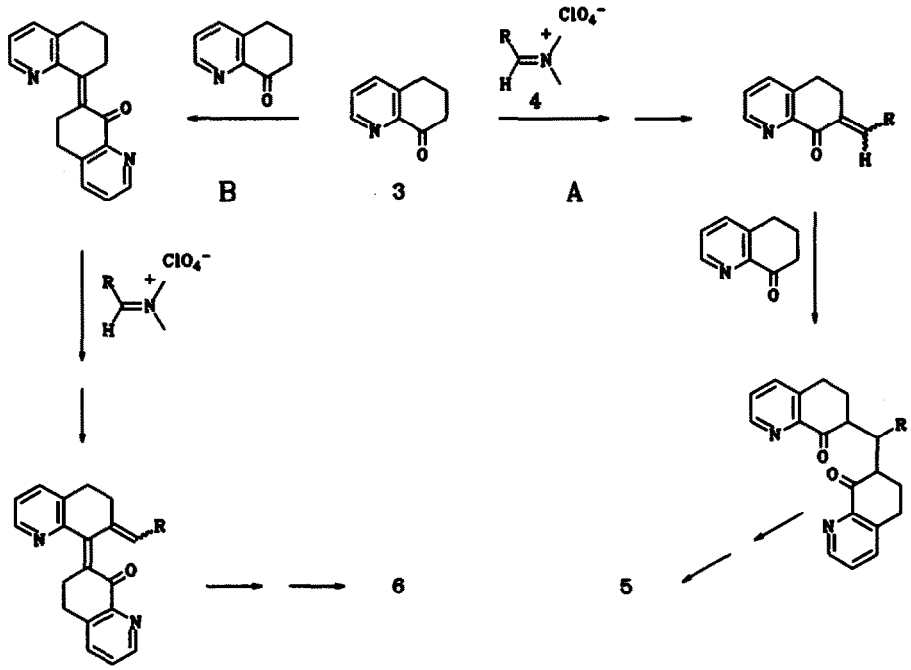
	R	yield (%)
5a/6a		28/31
5b/6b		49/10
5c/6c		20/25
5d/6d		trace/ 53
5e/6e		trace/ 38

Table 1. Some examples of terpyridines [8] **5, 6**

Thus, heating a mixture of two equivalents of ketone **3** [6a,9] and one equivalent of N,N-dimethyl-(4'-methoxy)benzylidene iminium perchlorate **4a** in the presence of ammonium acetate for 48h at 140 °C (argon atmosphere) results after workup [8] in the formation of a yellow brownish oil. After column chromatography (Al_2O_3, activity III, CH_2Cl_2/acetone 10:1) we isolated the expected 7-(4'-methoxy)phenyl-5,6,8,9-tetrahydroquino[8,7-b][1,10]phenanthroline **5a** in a moderate 26% yield (scheme 1). In addition,

we isolated another crystalline product, which showed the expected proton resonances. Nevertheless, we observed two sets of signals for both aromatic and aliphatic protons of the polycyclic carbon fragment. Additional spectroscopic analysis (nmr, ms, and x-ray crystallographic data [8]) enabled us to assign structure **6a** to this second fraction, 6-(4'-methoxy)phenyl-7,8,13,14-tetrahydroquino[8,7-k][1,8]phenanthroline.

As shown in table 1, the distribution of isomeric quino[1,x]phenanthrolines seems to depend strongly on the electronic and/or steric properties of the substituent in the native iminium compound. Thus, the more electron rich 4'-N,N-dimethylaminophenyl fragment predominantly produces the "U-shaped" isomer **5**, whereas the aliphatic isopropyl fragment nearly quantitatively gives the "S-shaped" type **6**.



Scheme 2. Proposed reaction mechanism and intermediates during the synthesis of substituted fused pyridines.

Our preliminary attempts to interpret the results of the above experiments is shown in scheme 2. We assume pathway A to be initiated by an aminoalkylation (Mannich reaction) of ketone **3** with the electrophilic iminium compound, leading to the hydroperchlorate salt of the corresponding Mannich base. These compounds are known for their thermal instability, especially in the case of the dimethylamino derivatives.[10] Under the current reaction conditions, they generate the Michael acceptor which is attacked by a further equivalent of ketone **3**. The resulting 1,5-diketone is condensed in situ with ammonia (e.g. from ammonium acetate). The intermediate dihydro pyridine cannot be isolated and is oxidized in the final step to the heteroaromatic system **5**. However, the initial step of pathway B seems to be an aldol condensation of two equivalents of ketone **3**. This intermediate may be attacked by the iminium compound leading to a vinylogous Mannich base. After the elimination of dimethylamine, Michael addition of ammonia, and cyclization results in the formation of **6**.

To our knowledge, no example of an aminoalkylation of a ketone by a preformed ternary iminium perchlorate has yet been described in the literature. Our preliminary attempts to use this type of iminium salts specifically for the preparation of Mannich bases by adapting one of the procedures known for the methylene iminium halides[11] have failed.

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REFERENCES AND NOTES

1. For example see: [1a]Thummel, R. P., *Synlett*, **1992**, 1-12; [1b]Vögtle, F., Lüer, I., Balzani, V., Armaroli, N., *Angew. Chem.*, **1991**, *103*, 1367-1369; *Angew. Chem. Int. Ed. Engl.*, *30*, 1333; [1c]Bell, T. W., Ludwig, R. T., Xiang, C. L., *J. Am. Chem. Soc.*, in print.
2. [2a]Ransohoff, J. E. B., Staab, H. A., *Tetrahedron Lett.*, **1985**, *26*, 6179-6182; [2b]Bell, T. W., Firestone, A., *J. Am. Chem. Soc.*, **1986**, *108*, 8109-8111.
3. Bell, T. W., Liu, J., *Angew. Chem.*, **1990**, *102*, 931-933; *Angew. Chem. Int. Ed. Engl.*, *29*, 923.
4. Hery, C. Ph. D., *Dissertation*, University of Houston, **1991.**
5. Hegde, V., Jahng, Y., Thummel, R. P., *Tetrahedron Lett.*, **1987**, *28*, 4023-4026.
6. [6a]Westerwelle, U., Esser, A., Risch, N., *Chem. Ber.*, **1991**, *124*, 571-576; [6b]Risch, N., Esser, A., *Synthesis*, **1988**, 337-339.
7. [8a]Leonard, N. J., Paukstelis, J. V., *J. Org. Chem.*, **1963**, *28*, 3021-3024; [8b]Leonard, N. J., Klainer, J. A., *J. Heterocycl. Chem.*, **1971**, *8*, 215-219.
8. The solvent is removed in vacuo. The residue is treated with water and conc. ammonia. The resulting crystalline powder is separated by filtration, solved in CH_2Cl_2 , and the solution is washed with water. After drying with sodium sulphate the solvent is removed, yielding the raw product as yellow-brownish oil. **5a**: mp >300°C. **6a**: mp 234-235°C. **5b**: mp 277°C (lit.[5]: 275-277°C); ^{1}H-NMR (300 MHz, $CDCl_3$/TMS), δ(ppm): 8.09 (dd, ^3J=3.8, ^4J=1.5 Hz, 2H), 7.57 (dd, ^3J=7.6, ^4J=1.5 Hz, 2H), 7.12 (m_c, 3H), 6.88 (d, ^3J=8.8 Hz, 2H), 3.07 (s, 6H, 2 CH_3), 2.92 (m_c, 8H, 4 CH_2). **6b**: ^{1}H-NMR (80 MHz, $CDCl_3$/TMS), δ(ppm): 8.57-8.75 (m, 2H), 7.45-7.64 (m, 4H), 7.10-7.27 (m, 2H), 6.72-6.84 (m, 2H), 3.55-3.74 (m, 2H, CH_2), 2.99 (s, 6H, 2 CH_3), 2.70-3.06 (m, 6H, 3 CH_2). **5c**: mp 259°C (lit.[5]: 255-257°C). **6c**: mp 281°C. **6d**: yellow needles, mp 206°C; ^{1}H-NMR (300 MHz, $CDCl_3$/TMS), δ(ppm): 8.75 (dd, ^3J=4.8, ^4J=1.7 Hz, 1H), 8.59 (dd, ^3J=4.8, ^4J=1.7 Hz, 1H), 7.61 (dd, ^3J=7.6, ^4J=1.7 Hz, 1H), 7.55 (m_c, 1H), 7.21 (m_c, 2H), 3.55 (m_c, 2H, CH_2), 3.47 (sept, ^3J=6.9 Hz, 1H, 7^1-H), 2.92 (m_c, 4H, CH_2-CH_2), 2.85 (m_c, 2H, CH_2), 1.46 (d, ^3J=6.9 Hz, 6H, 2 CH_3); MS (70 eV): m/z (%) = 328 (14), 327 (64,M^+), 326 (100), 312 (22), 310 (13), 156 (18). **6e**: mp 175-177°C.
   A more detailed discussion of the synthesis and features of substituted fused pyridines will be published elsewhere: N. Risch, U. Westerwelle, manuscript in preparation.
9. Thummel, R. P., Lefoulon, F., Cantu, D., Mahadevan, R., *J. Org. Chem.*, **1984**, *49*, 2208-2212.
10. Troschütz, R., Roth, H. J., *Arch. Pharm.*, **1978**, *311*, 406-414.
11. For example see: [11a]Kinast, G., Tietze, L. F., *Angew. Chem.* **1976**, *88*, 261-262; *Angew. Chem. Int. Ed. Engl.*, *15*, 239; [11b]Schreiber, J., Maag, H., Hashimoto, N., Eschenmoser, A., *Angew. Chem.*, **1971**, *83*, 355-357; *Angew. Chem. Int. Ed. Engl.*, *10*, 330; [11c]Jasor, Y., Gaudry, M., Luche, M. J., Marquet, A., *Tetrahedron*, **1977**, *33*, 295-303; [11d]Volz, H., Kiltz, H.-H., *Liebigs Ann. Chem.*, **1971**, *752*, 86-101; [11e]Esser, A., *Dissertation*, Universität Bielefeld, **1989**; [11f]Beugelmans, R., Benadjila-Iguertsira, L., Negron, G., Roussi, G., *Can. J. Chem.*, **1985**, *63*, 725-734.

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