

HETEROAROMATIC TRIPOLES. SYNTHESSES OF AMINOPYRIMIDINE-BISPYRIDINIUM SALTS AND BISPYRIDINIOPYRIMIDINAMINIDES

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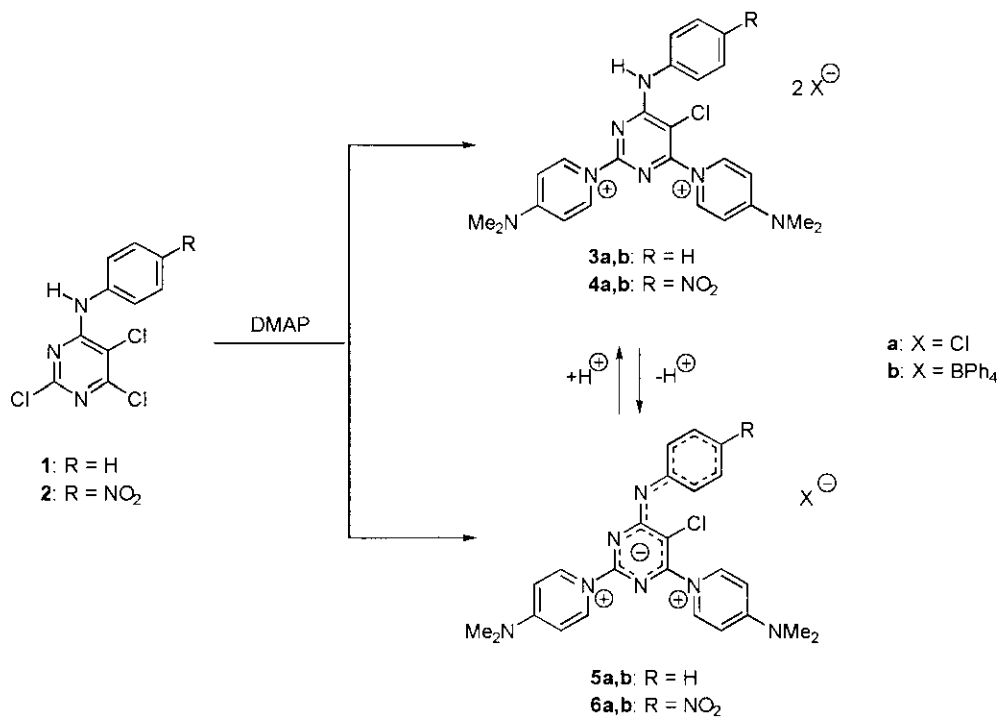
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Abstract - Depending on the substitution pattern of the 4-aminophenyl-trichloropyrimidine derivatives (**1**, **2**) reaction with 4-dimethylaminopyridine and 4-(pyrrolidin-1-yl)pyridine, respectively, formed either the pyrimidine-dipyridinium salts (**3**, **4**, **7**, **8**) or the tripolar species (**5**, **6**, **9**, **10**) which are the first examples of mesomeric betainium salts.

The synthesis of multiply charged heteroaromatics as potential semi-conductors,¹ precursors of novel polymers¹ and stable radicals,² acetylcholine esterase reactivators,³ herbicides⁴ and novel oxidizing agents⁵ has become a challenge in heterocyclic chemistry during the last years. On the other hand, considerable attention was recently concentrated upon the synthesis of pharmacologically interesting betaines with antiprotozoal and antibacterial activities.⁶ In general, compounds which combine charge-cumulated as well as betainic properties are very scarcely described in the literature.¹ We were interested in the synthesis of such molecules and chose trichloroaminopyrimidine derivatives as suitable starting materials. An additional stimulus for this work was the known activity of aminopyrimidines and of substances related to them, some of which occur in nature⁷ or were being developed as pharmaceutical agents.⁸ In continuation of our interest on betaines⁹ this paper describes dicationic aminopyrimidine dipyridinium salts and the first representatives of the new class of *heterocyclic mesomeric betainium salts*, tripolar dipyridiniopyrimidin-4-aminides.

The (4-aminophenylpyrimidine-2,6-diyl)-bispyridinium dichloride (**3a**)¹⁰ was obtained by chlorine displacement of the aminophenyltrichloropyrimidine (**1**)¹¹ with an excess of 4-dimethylaminopyridine in chlorobenzene at reflux temperature. Recrystallization of the crude reaction product from ethanol furnished **3a** as a colorless solid in 54% yield. Conducting the reaction in boiling anhydrous ethyl acetate with *in situ* interception of the leaving group by sodium tetraphenylborate produced the corresponding colorless BPh₄⁻ salt (**3b**) in 61% yield. Deprotonation of **3a,b** with 1,8-bis(dimethylamino)naphthalene (proton sponge[®]) in

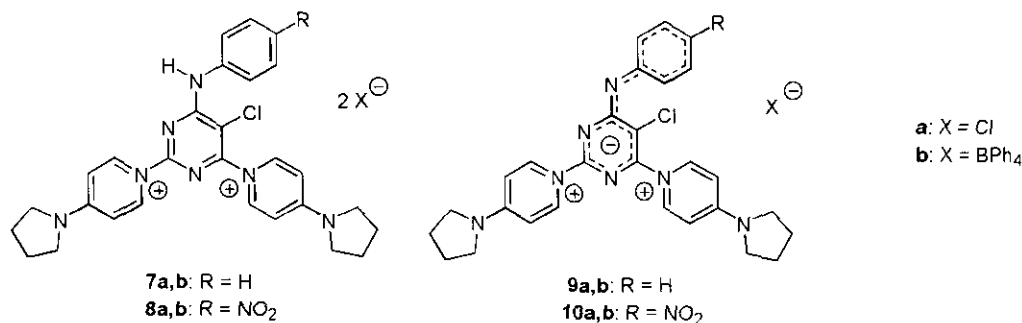
EtOH formed **5a,b** as intensely orange-colored and rather instable solids which reconstituted the dicationic species (**3a,b**) upon exposure to atmospheric moisture. In sharp contrast, substitution on the 4-nitrophenyl-trichloropyrimidine (**2**) applying the same reaction conditions resulted in the ready formation of the desired mesomeric betainium salts (**6a,b**)¹⁰ in one single step (45 and 52% yields, respectively). These intense orange-colored compounds were purified by recrystallization from ethanol and were found to be stable even upon heating. In accord with *Kröhnke's* rule which predicts increasing stabilization of N-ylides and related systems with increasing number of atoms involved in the negative charge delocalization,¹² the strongly electron-withdrawing nitro group of **6a,b** causes a considerable stabilization of the betainic structure. Protonation of **6a,b** (**6a**: HCl/EtOH; **6b**: HCl/EtOH, then NaBPh₄/EtOAc) yielded the corresponding bis-hetarenium salts (**4a,b**) which were recrystallized from ethanol to form light yellow crystals in nearly quantitative yield, respectively.



Scheme 1

The 1,1'-(4-aminophenylpyrimidine-2,6-diyl)-bis-4-(pyrrolidin-1-yl)pyridinium salts (**7a,b**, **8a,b**) and the 2,6-di-4-(pyrrolidin-1-yl)pyridinopyrimidin-4-aminides (**9a,b**, **10a,b**) were obtained starting with 4-(pyrrolidin-1-yl)pyridine and the trichloropyrimidines (**1**) and (**2**), respectively.¹⁰ The chloride (**7a**) was formed as a light yellow solid in chlorobenzene at reflux temperature for 15 min (77% yield). *In situ* anion exchange to tetraphenylborate in EtOAc at 77°C gave the nearly colorless **7b** in 54% yield. Deprotonation of **7a** with proton sponge in EtOH/EtOAc formed the betainium chloride (**9a**) (76%) as an instable yellow solid,

whereas the corresponding lemon-yellow tetraphenylborate (**9b**) (67%) proved to be stable against air and moisture. Similarly to the DMAP series mentioned above, the 4-nitrophenylpyrimidine derivative (**2**) formed the orange-colored betaines (**10a,b**) (78% and 64%, respectively) which were protonated (**10a**: HCl/EtOH; **10b**: HCl/EtOH, then NaBPh₄/EtOAc) to form the dicationic species (**8a,b**) as nearly colorless compounds in 89% and 81% yield, respectively.



Scheme 2

The tripolar structures (**5**, **6**, **9**, and **10**) are unusual hybrids between hetarenium salts and mesomeric betaines as they possess two positive charges on the pyridinium rings and one negative charge which is delocalized within the central pyrimidin-4-aminide moieties and the either *E* or *Z* oriented phenyl rings. Thus, they are the first representatives of a new class of compounds - mesomeric betinium salts - anticipated to have interesting spectroscopic and chemical properties. In accordance with the cross-conjugation between the cationic and the anionic segments of the molecule, upon betaine formation the pyridinium ¹H NMR chemical shifts of the dicationic species (**3**, **4**, **7**, and **8**) were relatively unaffected, whereas the resonances of the phenyl protons shift upfield [eg. **3a** to **4a**: $\Delta\delta(o\text{-H}) = -0.23$ ppm] due to the diminished overall-charge of the betainic systems. Correspondingly, the NH signals [10.48 - 10.91 ppm] disappeared and a hypsochromic shift of the absorption maxima was observable in UV spectroscopy [eg. **4a**: $\lambda_{\text{max}}(\text{MeCN}) = 329.60$ nm; **6a**: $\lambda_{\text{max}}(\text{MeCN}) = 319.00$ nm].

REFERENCES AND NOTES

1. A. S. Koch, A. S. Feng, T. A. Hopkins, and A. Streitwieser, *J. Org. Chem.*, 1993, **58**, 1409; S. G. DiMagno, K. C. Waterman, D. V. Speer, and A. Streitwieser, *A. J. Am. Chem. Soc.*, 1991, **113**, 4679.
2. Y. Ikegami, T. Muramatsu, and K. Hanaya, *J. Am. Chem. Soc.*, 1989, **111**, 5782.
3. Y. Ashani, S. Cohen, *J. Med. Chem.*, 1971, **14**, 621; C. F. Barfknecht, F. W. Benz, and J. P. Long, *J. Med. Chem.*, 1971, **14**, 1003; C. N. Corder and J. L. Way, *J. Med. Chem.*, 1966, **9**, 638.
4. W. R. Boon, *Chem. Ind. (London)*, 1965, 782; A. D. Dodge, *Endeavour*, 1970, **111**, 130; A. L. Black and L. A. Summers, *J. Chem. Soc. C.*, 1969, 610; E. C. Campbell, E. E. Glover, and G. Trenholm, *J. Chem. Soc.*, 1969, 1987.

5. R. Weiß, R. May, and B. Pohmrehn, *Angew. Chem.*, 1996, **108**, 1319; *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1232.
6. E. Alcalde, L. Pérez-García, I. Dinarés, and J. Frigola, *Chem. Pharm. Bull.*, 1995, **43**, 493; E. Alcalde, L. Pérez-García, I. Dinarés, G. H. Coombs, and J. Frigola, *Eur. J. Med. Chem.*, 1992, **27**, 171; E. Alcalde, I. Dinarés, and J. Frigola, *Eur. J. Med. Chem.*, 1991, **26**, 633.
7. D. J. Brown, 'Comprehensive Heterocyclic Chemistry,' Vol. 3, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, New York, 1984, pp. 57 - 155.
8. *c.f.* M. A. Fischl, G. M. Dickinson, and L. La Voie, *J. Am. Med. Assoc.* 1988, **259**, 1185; C. Lepout, R. Raffi, S. Metheron, C. Katiana, B. Regnier, A. G. Simot, C. Marche, C. Vederenne, and J. L. Vilde, *Am. J. Med.* 1988, **84**, 94; C. J. Allegra, J. A. Kovacs, J. C. Drake, J. C. Swan, B. A. Chabner, and H. Masur, *J. Clin. Invest.* 1987, **79**, 478; J. A. Kovacs, C. J. Allegra, J. C. Swan, J. C. Drake, J. E. Parillo, B. A. Chabner, and H. Masur, *Antimicrob. Agents Chemother.* 1988, **32**, 430.
9. A. Schmidt and M. K. Kindermann, *J. Org. Chem.*, 1997, **62**, 3910; A. Schmidt and A. Hetzheim, *Tetrahedron* 1997, **53**, 1295; A. Schmidt, A. Hetzheim, and D. Albrecht, *Heterocycles*, 1996, **43**, 2153.
10. Selected physical data of representative compounds (NMR measured in DMSO- d_6 , melting points are uncorrected): **3a**, decomp (EtOH) > 224°C; $^1\text{H NMR}$: δ = 3.32 (s, 6H), 3.35 (s, 6H), 7.41 (m, 9H), 8.63 (d, J = 8.1 Hz, 2H), 8.87 (d, J = 8.1 Hz, 2H), 10.48 (s, 1H); **3b**: mp (EtOH) 138°C; **4a**, slow decomp (EtOH) > 240°C; $^1\text{H NMR}$: δ = 3.37 (s, 6H), 3.41 (s, 6H), 7.26 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 8.02 (d, J = 9.3 Hz, 2H), 8.37 (d, J = 9.3 Hz, 2H), 8.67 (d, J = 8.1 Hz, 2H), 8.97 (d, J = 8.1 Hz, 2H), 10.91 (s, 1H); **4b**, mp (EtOH) 159 - 161°C; **5a**, decomp > 215°C; **5b**, mp 127°C, $^1\text{H NMR}$: δ = 3.25 (s, 6H), 3.28 (s, 6H), 6.78 (t, J = 7.2 Hz, 8H), 6.92 (t, J = 7.2 Hz, 16H), 7.05 (d, J = 8.3 Hz, 2H), 7.09 (t, J = 8.2 Hz, 2H), 7.17 (m, 19H), 7.23 (d, J = 8.2 Hz, 2H), 8.58 (d, J = 7.8 Hz, 2H), 8.85 (d, J = 8.4 Hz, 2H); **6a**, mp (EtOH) > 300°C; $^1\text{H NMR}$: δ = 3.29 (s, 6H), 3.32 (s, 6H), 7.19 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 8.29 (d, J = 8.8 Hz, 2H), 8.61 (d, J = 8.0 Hz, 2H), 8.93 (d, J = 8.2 Hz, 2H); **6b**, mp 249 - 253°C; **7a**, mp (EtOH) > 300°C; $^1\text{H NMR}$: δ = 2.08 (m, 8H), 3.68 (m, 8H), 7.09 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 7.34 (tt, J = 8.3/1.1 Hz, 1H), 7.52 (t, J = 8.3 Hz, 2H), 7.63 (dd, J = 8.3/1.3 Hz, 2H), 8.65 (d, J = 7.9 Hz, 2H), 8.89 (d, J = 8.1 Hz, 2H), 10.49 (s, 1H); **7b**, mp 239 - 243°C; **8a**, slow decomp (EtOH) > 243°C; $^1\text{H NMR}$: δ = 2.07 (m, 8H), 3.70 (m, 8H), 7.11 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 8.01 (d, J = 9.0 Hz, 2H), 8.35 (d, J = 9.0 Hz, 2H), 8.65 (d, J = 7.8 Hz, 2H), 8.97 (d, J = 8.1 Hz, 2H), 10.78 (s, 1H); **8b**, mp 283 - 285°C; **9a**: no defined mp due to decomp.; **9b**, mp 238 - 241°C; **10a**, decomp > 220°C, $^1\text{H NMR}$: δ = 2.08 (m, 8H), 3.69 (m, 8H), 7.10 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 7.96 (br d, 2H), 8.36 (d, J = 9.0 Hz, 2H), 8.66 (d, J = 7.9 Hz, 2H), 8.98 (d, J = 8.1 Hz, 2H), 10.88 (s, 1H); **10b**, mp 245 - 251°C.
11. H. Ackermann and P. Dussy, *Helv. Chim. Acta*, 1962, **45**, 1683.
12. I. Zugravesku and M. Petrovanu, 'N-Ylid Chemistry,' McGraw-Hill International Book Company, New York, 1976.

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