Stanislav Kafka*

Department of Food Engineering and Chemistry, Faculty of Technology, Tomas Bata University in Zlin, CZ-76272 Zlin, Czech Republic

Barbara Larissegger-Schnell and Thomas Kappe

Department of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens-University of Graz, Heinrichstr. 28, A-8010 Graz, Austria

Received April 13, 2004

Dedicated to Professor Peter Stanetty, Vienna University of Technology, on the occasion of his 60th birthday

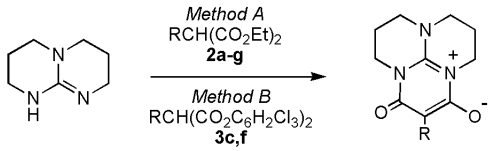
The synthesis of seven mesomeric triazaphenalene betaines **4a-g** by condensation reaction of hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine **1** with diethyl malonates **2a-g** or with bis(2,4,6-trichlorophenyl)malonates **3c,f** has been achieved. The guanidine **1** forms in benzene solution a salt with trimethyl methanetricarboxylate **5** which upon heating produces **4a**.

J. Heterocyclic Chem., **41**, 717 (2004).

The rapid development and expansion of the chemistry of six-membered mesoionic heterocycles started in 1971 when almost simultaneously the first general syntheses of mesoionic 4,6-dioxopyrimidines were published, and their usefulness in 1,4-dipolar cycloaddition reactions was demonstrated [2,3]. This class of compounds is usually obtained from reactive malonic acid derivatives such as malonyl chlorides, their substituted derivatives are actually chlorocarbonyl ketenes [4], AME's (= active malonic esters, 2,4,6-bis-trichlorophenyl malonates, "magic malonates") [5], or carbon suboxide (C_3O_2) [6], especially for derivatives which are unsubstituted at the malonyl carbon atom. In order to form six-membered rings the substrates have to be 1,3-dinucleophiles. These can be N,N'-disubstituted amidines, leading to mesomeric pyrimidine betaines, N-substituted amides leading to 1,3-oxazine betaines, N-substituted thioamides leading to 1,3-thiazine betaines, or 1,2,3-triazenes yielding 1,2,3-triazines [7-9]. The chemistry of these compounds has been extensively reviewed twenty years ago [8,9]. New results in this area have been mainly concerned with the syntheses of compounds with new medicinal and biological activities [10], or as building blocks (in combination with nitronyl nitroxide radicals) for their use in material sciences [11]. Gotthard has shown in a number of papers that mono- and bicyclic six-membered mesoions can undergo 1,4-dipolar cycloaddition reactions with singlet oxygen as well as with electron-poor and electron-rich double bond systems [12]. Potts and Padwa have demonstrated that intramolecular cycloadditions can lead to interesting new ring systems [13]. Some results concerning cycloaddition reactions as well as rearrangement reactions have been published from our laboratory [14,15].

In the present paper we describe the synthesis of triazaphenalene cross-conjugated mesomeric zwitterions starting with the commercially available hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine **1** [16]. Heating this compound with diethyl malonates **2a-g** in an oil bath to about 150-180 °C without solvent, permitting the formed ethanol to distill off, leads to the betaines **4a-g** in good yields. However, performing the reaction in boiling bromobenzene (bp. 156 °C) for about 4-6 hours is more convenient, Method A. As pointed out in the introduction, this type of mesomeric betaines has been obtained so far only with the help of chlorocarbonyl ketenes, "magic malonates" or carbon suboxide. For instance, a number of fused mesoionic 1,3-diazines have been obtained from aromatic guanidines, such 1,1-diethyl-2,3-diphenylguanidine [17], N-substituted 2-aminopyrimidines [10a,18,19] or similar 2-amino heterocycles [10b,15,20] using bis-(2,4,6-trichlorophenyl)malonates [5]. Our substrate **1** represents a N,N',N''-trisubstituted guanidine which is symmetric and bears only aliphatic substituents. The latter makes it a very good nucleophile which reacts with dialkyl malonates at about 150 °C without the formation of side products. We have of course also tried the reaction with two magic malonates (**3 c**,**f**) under standard conditions at 220-240 °C without solvent (Method B), however, the yields of **4c,f** were much lower, which is explained by the fact that trichlorophenol is a very good solvent for polar compounds and not easily removed.

Scheme 1



2,3,4	R
a	H
b	CH_3
c	C_4H_9-n
d	C_4H_9-t
e	CH_2Ph
f	Ph
g	$C_6H_2(CH_3)_3$

It has been known for some time that pyrimidine betaines can be obtained with diethyl malonates from amidine systems, for instance from N-substituted 2-aminopyridines, in moderate yield [15,19]. However, six-membered mesomeric betaines can undergo at elevated temperatures various rearrangement reactions [8,9]. Oxazines and thiazines may loose carbon dioxide or carbonyl sulfide while N-aryl-pyrimidines loose arylisocyanates leading to carbonyl ketenes which in many cases undergo intramolecular ringclosure reactions (Type A rearrangements [9,21,22]). Yvette Issac [15] has shown that diethyl malonates give with *N*-alkyl-2-aminopyridines in boiling tetraline (bp. 207 °C) mesoionic pyrido[1,2-*a*]pyrimidin-1-ium-2-olates, while under the same conditions with *N*-alkyl(phenyl)-*N*'-phenyl-benzamidines rearrangement occurs (with loss of phenylisocyanate) to yield the expected 4-quinolones [21-23]. Furthermore, fused pyrimidine betaines can rearrange at higher temperatures *via* 2-oxo-ketenes to thermodynamically more stable isomers (Type B rearrangements). [1,8,9,19,21,23-25]. Under these conditions the bicyclic guanidine **1** meets the requirements for a perfect substrate: the high nucleophility allows a rather low reaction temperature (150 °C), the lack of aromatic substituents (even an attackable C-atom within the system [1,19,24] prevents the formation of side products by decompostion and rearrangement reactions. Compounds **4** are stable up to 250 °C, some melting points with decomposition are at about 300 °C.

Triethyl- and trimethyl methanetricarboxylates **5** are very valuable malonic esters allowing the introduction of an ester group in the 2-position of a malonyl heterocycle [26,27] or even into a rearranged product of that heterocycle [15]. Moreover these esters are more reactive than alkyl or aryl substituted malonates, compare for instance the temperature of the reaction of **6** to **4a** (110 °C) with that of Method A for **1** + **2b-g** to give **4b-g** (150 °C). Furthermore **5** is a stronger acid (pk_a 10.81 in DMSO [28]) than diethyl malonate (pk_a 13.3).

Guanidines are known to be strong bases (pk_a for the protonated guanidine itself is 13.5 [29]), for compound **1** a pk_a value of 11.22 (in acetic acid!) has been determined [30]. It is therefore not surprising that we observed a salt formation **6** when **1** and **5** were dissolved in benzene (**5** should be even a stronger acid in benzene [31]). The complex **6**, which might be stabilized by hydrogen bridges, can be recrystallized from benzene and has a melting point of 129-131 °C under decomposition. However, heating of **6** in toluene (bp 110 °C) converted it to **4a** in 75 minutes. The unsubstituted substance **4a** can be obtained from **1** and **5** as well as with the unsubstituted malonate **2a**.

At the present time we can not answer the question by what mechanism the ester group in the expected compound **4** (with R = CO_2CH_3) has been eliminated. The loss of the methoxycarbonyl group is surprising, because 2-amino-pyridine, 2-aminothiazole, 2-aminobenzothiazole and even 2-aminopyrimidine, which is also a guanidine derivative, afforded with trimethyl methanetricarboxylate stable esters [27]. We have found by GC-MS analysis, that dimethyl carbonate is formed as the product of elimination besides the compound **4a** under anhydrous conditions, whereas carbon dioxide is evolved in the presence of moisture. On the other hand we have prepared also pseudo-cross-conjugated mesomeric zwitterions from triethyl methanetricarboxylate and pyrazoles with an intact ester group [26b].

The nmr data of the unsubstituted compound **4a** are comprised in Figure 1. The proton and carbon assignments are based on HMBC (heteronuclear multiple bond correlation) experiments. The high symmetry of the molecule is shown by the fact that there are only 6 signals in the ^{13}C nmr and 4 signals in the ^{1}H nmr spectrum. The spectra of some mesoionic pyrimido betaines have been studied previously [32,33], and it has been shown that the malonyl C-atom is found between 81.0 and 96.5 ppm and that the C-atom in the positively charged amidinium system appears at 154.2-157.2 ppm, the C=O, respectively C-O^- signal appears at 154.2-156.3 ppm. Our value for the C-atom in the negatively charged carbonyl-enolat system at 75.84 ppm is somewhat lower than usual values suggesting a stronger polarization. On the other hand the low value of 148.32 ppm at the central C-atom indicates that the positive charge is distributed over the whole guanidinium part of the molecule.

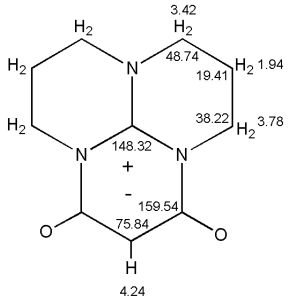


Figure 1. Proton and carbon assignments of compound **4a** based on HMBC experiments.

Scheme 2

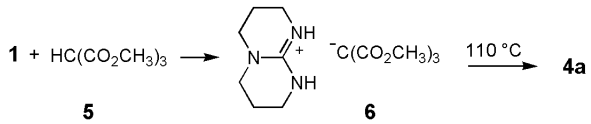


Table 1

Physical and Analytical Data of 2-R-3-oxo-hexahydro-3*H*-3a,6a,9a-triazaphenalen-9a-ium-1-olates **4**

Comp. No.	R	Method Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) C	H	N
4a	H	C: 67 [a]	290-303 [c] (ethanol)	$C_{10}H_{13}N_3O_2$	57.96 57.57	6.32 6.28	20.28 20.13
4b	CH_3	A: 82	265-269 [c] (ethanol)	$C_{11}H_{15}N_3O_2$	59.71 59.40	6.83 7.05	18.99 18.67
4c	*n*-C_4H_9	A: 80 B: 52 C: 91 [a]	202-206 (acetone)	$C_{14}H_{21}N_3O_2$	63.85 63.47	8.04 7.90	15.96 15.68
4d	t-C_4H_9	A: 77	235-240 (AcOEt)	$C_{14}H_{21}N_3O_2$	63,85 63.57	8.04 7.81	15.96 15.64
4e	$CH_2C_6H_5$	A: 79	229-234 (1-butanol)	$C_{17}H_{19}N_3O_2$	68.67 68.31	6.44 6.50	14.13 13.85
4f	C_6H_5	A: 83 B: 46 C: 92 [a]	263-266 (ethanol)	$C_{16}H_{17}N_3O_2$	67.83 67.80	6.05 6.00	14.83 14.68
4g	$C_6H_2(CH_3)_3$ [b]	A: 64	335-340 [c] (1-butanol)	$C_{19}H_{23}N_3O_2$	70.13 69.88	7.12 6.79	12.91 12.59

[a] Method C: Heating of **1** and **2** without solvent; [b] R = 2,4,6-trimethylphenyl; [c] melting under decomposition.

Table 2

Spectroscopic Data of Compounds **4**

Compound No.	IR (in KBr) $\tilde{\nu}$ (cm^{-1})	^{1}H-NMR (in DMSO-d_6) δ (ppm)
4a	3600-2900b,m, 1647s, 1600s, 1450w, 1383w, 1367m, 1327s	1.94 (tt, 4H, H-5 + H-8, *J* = 5.7 Hz, 5.7 Hz), 3.42 (t, 4H, H-6 + H-7, *J* = 5.7 Hz), 3.78 (t, 4H, H-4 + H-9, *J* = 5.7 Hz), 4.24 (s, 1H, H-2)
4b	3500-3000mb, 1637s, 1591s, 1456m, 1421m, 1362m	1.64 (s, CH_3), 1.94 (tt, 4H, H-5 + H-8, *J* = 5.7 Hz, 5.7 Hz), 3.41 (t, 4H, H-6 + H-7, *J* = 5.7 Hz), 3.82 (t, 4H, H-4 +H-9, *J* = 5.7 Hz)
4c	2950m, 2920m, 2865m, 1632s, 1580s, 1570s, 1526w, 1540w, 1420w, 1383s	in deuteriochloform: 0.87 (t, 3H, CH_3, *J* = 7.0 Hz), 1.24-1.50 (m, 4H, CCH_2CH_2C), 2.07 (tt, 4H, H-5 + H-8, *J* = 5.6 Hz, 5.6 Hz), 2.36 (t, 2H, H-1 of butyl, *J* = 7.5 Hz), 3.46 (t, 4H, H-6 + H-7, *J* = 5.6 Hz), 4.03 (t, 4H, H-4 + H-9, *J* = 5.6 Hz)
4d	2990w, 2950m, 2915m, 2905m, 1612sb, 1538s, 1455m, 1350w, 1325m	1,29 (s, 9H, 3xCH_3), 1.93 (tt, 4H, H-5 + H-8, *J* = 5.6 Hz, 5.6 Hz), 3.38 (t, 4H, H-6 + H-7, *J* = 5.6 Hz), 3.76 (t, 4H, H-4 + H-9, *J* = 5.6 Hz)
4e	3010w, 2940m, 2905m, 2870w, 1635sb, 1590s, 1525m	1.96 (tt, 4H, H-5 + H-8, *J* = 5.6 Hz, 5.6 Hz), 3,42 (t, 4H, H-6 + H-7, *J* = 5.6 Hz), 3.65 (s, CH_2 of benzyl), 3.75 (t, 4H, H-4 + H-9, *J* = 5.6 Hz), 7.02-7.40 (m, 5H, ArH)
4f	2940w, 2890w, 2875w, 1660s, 1617s, 1593s, 1530m, 1500w	2.01 (tt, 4H, H-5 + H-8, *J* = 5.5 Hz, 5.5 Hz), 3.36 (t, 4H, H-6 + H-7, *J* = 5.5 Hz), 3.88 (t, 4H, H-4 + H-9, *J* = 5.5 Hz), 7.00 (t, 1H, H-4 of phenyl, *J* = 7.5 Hz), 7.17 (dd, 2H, H-3 of phenyl + H-5 of phenyl, *J* = 7.5 Hz, 7.5 Hz), 7.61 (d, 2H, H-2 of phenyl + H-6 of phenyl, *J* = 7.5 Hz) in deuteriochloroform: 2.04 (tt, 4H, H-5 + H-8, *J* = 5.5 Hz, 5.5 Hz), 3.33 (t, 4H, H-6 + H-7, *J* = 5.5 Hz), 4.04 (t, 4H, H-4 + H-9, *J* = 5.5 Hz), 7.09 (t, 1H, H-4 of phenyl, *J* = 7.0 Hz), 7.28 (dd, 2H, H-3 of phenyl + H-5 of phenyl, *J* = 7.0 Hz, 7.0 Hz), 7.70 (d, 2H, H-2 of phenyl + H-6 of phenyl, *J* = 7.0 Hz)
4g	3020-2820wb, 1620s, 1590sh, 1528m, 1488m, 1455m, 1438m	1.96-2.01 (m, 9H, 3xCH_3), 2.19 (tt, 4H, H-5 + H-8, *J* = 6.0 Hz, 6.0 Hz), 3.46 (t, 4H, H-6 + H-7, *J* = 6.0 Hz), 3.86(t, 4H, H-4 + H-9, *J* = 6.0 Hz), 6.75 (s, 2H, 2ArH)

EXPERIMENTAL

Melting points were determined on a Gallencamp melting point apparatus, Mod MFB-595 in open capillary tubes. IR spectra were recorded on a Perkin Elmer 298 spectrometer or a Galaxy Series FTIR 7000 in potassium bromide pellets. ^{1}H nmr spectra were recorded on a Varian Gemini 200 instrument or an AVANCE DRX 500 at 500 MHz (for **4a**,**b**,**d**,**g**). The ^{13}C nmr spectrum and the HMBC experiments for **4a** were performed with the same instrument. Chemical shifts are given on the δ scale (ppm). Microanalyses were performed on a C,H,N-automate Carlo Erba 1106 or a Fisons elemental analyzer, Mod. EA

1108. The purity of substances was checked by thin-layer chromatography on TLC aluminum sheets silica gel 60 F_{254}, No. 5554 (E. Merck, Darmstadt) using uv light (254 and 366 nm) for detection.

General Procedures for the Preparation of 2-R-3-oxo-hexahydro-3*H*-3a,6a,9a-phenalen-9a-ium-3-olates **4**.

Method A.

The mixture of hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine **1** [16] (30 mmoles) and the appropriate diethyl malonates **2** (40 mmoles) in 30 mL bromobenzene was refluxed for 4-6 hours. After cooling the mixture was diluted with diethyl ether. The solid product was filtered and recrystallized from the solvents given in Table 1.

Method B.

Examples: The mixture of **1** (1.39 g, 10 mmoles) and bis-(2,4,6-trichlorophenyl)-butylmalonate **3c** (5.19 g, 10 mmoles) was heated in an open flask in an oil bath to 220-240 °C for 30 minutes and left to get cold. The material was triturated with diethyl ether (30 mL) and the suspension filtered. The filter cake was washed with another portion of diethyl ether (20 mL) and subsequently three times shortly boiled with tetrachloromethane (25 mL) and filtered after cooling. The obtained single product (TLC) afforded after crystallization from acetone 1.36 g (52 %) of **4c**.

Compound **4f** was obtained from **1** and **3f** in a similar fashion. However, the working up procedure was modified: The reaction mixture was twice recrystallized from ethanol (30 mL and 50 mL) yielding 46 % of pure **3f**, mp 263-266 °C.

Method C

Examples: The mixture of compound **1** (1.39 g, 10 mmoles) and diethyl *n*-butylmalonate **2c** (2.16 g, 10 mmoles) was heated in an open flask in an oil bath with a heating rate of approximately 6 °C/min to 240 °C. The reaction started at 148 °C indicated by the evolution of ethanol. Boiling of the mixture ceased only in the final stage of heating. The residual block stuff was powdered and washed with diethyl ether (20 mL) affording 2.46 g (91 %) of substance **4c** identical (^{1}H nmr, and ir spectra, mp, tlc) with the compound obtained by methods A or B.

Compound **4f** was obtained from **1** and **2f** in a similar way: The mixture of **1** (1.39 g, 10 mmoles) and **2f** (2.36 g, 10 mmoles) was heated in an open flask in an oil bath at 110-120 °C for 1 hour. During this time the originally clear liquid boiled, crystals were formed, and the liquid phase continuously disappeared. The residue (2.60 g, 92 %) was actually pure **4f**; it was crystallized from ethanol affording 1.88 g (66 %) analytical pure **4f**.

Octahydro-pyrimido[1,2-*a*]pyrimidin-1-ium Tris(methoxycarbonyl)methanide (**6**).

The benzene solution of trimethyl methanetricarboxylate **5** (5.70 g, 30 mmoles) in benzene (50 mL) was added to a stirred solution of 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine **1** (4.18 g, 30 mmoles) dissolved in the same solvent (100 mL). Colorless crystals appeared within several seconds. The mixture was shortly boiled and a clear yellowish solution was formed. Colorless crystals of **6** precipitated on cooling were collected by filtration and were used in the further reaction without purification (mp 120-128 °C, yield 8.93 g, *i.e.* 90 %). A sample (0.33 g) of this substance afforded 0.28 g (77 % on reactants) of analytical pure **6**, colorless crystals, mp 129-131 °C dec (benzene); ir: 3660-2800 b, 2959 w, 1689 s, 1626 s, 1587 m, 1444 m; ^{1}H nmr in DMSO-d_6: δ 1.90 (tt, 4H, H-3 + H-7, *J* = 6.0 Hz, 6.0 Hz), 3.21 and 3.30 (2t, 2 x 4H, H-2, -4, -6, -8, *J* = 6.0 Hz), 3.39 (s, 9H, 3 CH_3), 7.77 (s, 2H, 2 NH); ^{1}H nmr in $CDCl_3$: δ 2.00 (tt, 4H, H-3 + H-7, *J* = 6.0 Hz, 6.0 Hz), 3.31 (m, 8H, H-2, -4, -6, -8), 3.62 (s, 9H, 3 CH_3), 7.30 (s, 2H, 2 NH).

Anal. Calcd. for $C_{14}H_{23}N_3O_6$: C, 51.06; H, 7.04; N, 12.76. Found: C, 50.69; H 7.28; N, 13.08.

Preparation of Compound **4a** by Reaction of **1** with Trimethyl Methanetricarboxylate **5** (Method C).

The mixture of pyrimido-pyrimidine **1** (1.39 g, 10 mmoles) with trimethyl methanetricarboxylate **5** (1.90 g, 30 mmoles) was heated in an open flask in an oil bath. The solid dissolved with increasing of the temperature at about 130 °C. At 132 °C vigorous gas evolution started and the remaining reaction mixture crystallized completely during two minutes. The bath temperature was kept at 139-140 °C for another 5 minutes, whereupon the substance was left to get cold. The crude product (2.20 g) was crystallized from ethanol to afford colorless crystals of **4a** (1.36 g, 66%). Physical data and spectra see Table 1 and 2.

Substance **4a** was also obtained by Method C from **1** and **2a** in a similar way (without the use of a solvent). The yield was 67 %.

Preparation of Compound **4a** by Decomposition of Complex **6**.

The solution of compound **6** (3.29 g, 10 mmoles) in toluene (20 mL) was refluxed until complex **6** disappeared from the reaction mixture according to tlc (75 minutes). During the reaction white crystals of the product precipitated from the originally clear boiling solution. After cooling the filtration afforded 1.19 g (57 %) of colorless crystals of **4a**.

Acknowledgements.

This study was supported by the ministry of Education, Youth and Sports of the Czech Republic (Grant No. MSM 265200015). We thank also Dr. Yvette Issac for the synthesis of compound **4g**.

REFERENCES AND NOTES

[1] Cross-conjugated and pseudo-cross-conjugated mesomeric betaines. Part 21; Part 20: B. Schnell and T. Kappe, *ECSOC-4*; www.unibas.ch/mdpi/ecsoc-4/a0065/a0065.htm (2000).

[2a] K. T. Potts and M. Sorm, *J. Org. Chem.*, **36**, 8 (1971); [b] K. T. Potts and M. Sorm, *J. Org. Chem.* **37**, 1422 (1972); [c] K. T. Potts and R. K. C. Hsia, *J. Org. Chem.*, **38**, 3485 (1973).

[3a] T. Kappe and W. Lube, *Monatsh. Chem.*, **102**, 781 (1971); [b] T. Kappe, P. F. Fritz and E. Ziegler, *Monatsh. Chem.*, **102**, 412 (1971); [c] T. Kappe and W. Lube, *Angew. Chem., Internat. Edit. (Engl.)*, **10**, 925 (1971).

[4] T. Kappe, Chlorocarbonylketenes, Encyclopaedia of Reagents in Organic Synthesis (EROS); (L. A. Paquette, Ed.) John Wiley & Sons, Chichester - New York - Brisbane - Toronto - Singapore, 1995, Vol. **2**, 1098-1100.

[5] T. Kappe, Bis-(2,4,6-trichlorophenyl)-malonates, AME's, Magic malonates, *EROS*, 1995, Vol. **1**, 577-579.

[6a] T. Kappe, Carbon Suboxide, *EROS*, 1995, Vol. **2**, 996-997; [b] HOUBEN-WEYL: Methoden der Organischen Chemie, G. Thieme Verlag, Stuttgart - New York, 1993, **E15**, 3119-3145.

[7] T. Kappe, W. Golser and W. Stadlbauer, *Chem. Ber.*, **111**, 2173 (1978).

[8] W. Friedrichsen, A. Böttcher and T. Kappe, *Heterocycles*, **19**, 1083 (1982).

[9] T. Kappe, *Lect. Heterocyclic Chem.*, **7**, 107-119 (1984).

[10a] R. A. Glennon, S. M. Tejani-Butt, W. Padgett and J. W. Daly, *J. Med. Chem.*, **27**, 1364 (1984); [b] G. O. Mbagwu, B. Bullock and O. Greer, *J. Heterocyclic Chem.*, **25**, 475 (1988); [c] G. O. Mbagwu and R. Garland, *J. Heterocyclic Chem.*, **25**, 571 (1988); [d] C. O. Kappe and T. Kappe, *Arch. Pharm. (Weinheim, Ger.)*, **324**, 863 (1991).

[11] S. Greve, C. Näther and W. Friedrichsen, *Org. Letters*, **2**, 2269 (2000).

[12a] H. Gotthardt and K.-H. Schenk, *Tetrahedon Lett.*, **24**, 4669 (1983); [b] H. Gotthardt and M. Riegels, *Chem. Ber.*, **121**, 1143 (1988); [c] H. Gotthardt and J. Blum, *Chem. Ber.*, **119**, 1445 (1986); [d] H. Gotthardt and K.-H. Schenk, *Chem. Ber.*, **118**, 4567 (1985); [e] H. Gotthardt and K.-H. Schenk, *Angew. Chem., Int. Ed. Eng.*, **24**, 608 (1985); [f] H. Gotthardt and J. Blum, *Chem. Ber.*, **120**, 109 (1987); [g] H. Gotthardt and J. Blum, *Chem. Ber.*, **118**, 4578 (1985), **120**, 115 (1987), **121**, 1579 (1988).

[13a] K. T. Potts and M. O. Dery, *J. Chem. Soc., Chem. Commun.*, 565 (1986); [b] K. T. Potts and M. O. Dery, *J. Org. Chem.*, **55**, 2884 (1990); [c] K. T. Potts, T. Rochanapruk, S. J. Coats, L. Hadjiarapoglou and A. Padwa, *J. Org. Chem.*, **58**, 5040 (1993); [d] A. Padwa, S. J. Coats and M. A. Semones, *Tetrahedron Lett.* **34**, 5405 (1993); [e] A. Padwa, D. J. Austin, A. T. Price and M. D. Weingarten, *Tetrahedron*, **52**, 3247 (1996).

[14a] T. Kappe and D. Pocivalnik, *Heterocycles*, **20**, 1367 (1983); [b] T. Kappe, W. Lube, K. Thonhofer, C. Kratky and U. G. Wagner, *Heterocycles*, **40**, 681 (1995).

[15]Y. A. El-Sayed Issac, *Bull. Chem. Soc. Jpn.*, **72**, 503 (1999); work performed at the Univ. of Graz, Austria, 1994-1995; including results of [21] and [32].

[16] Aldrich Handbook of Fine Chemicals, 2003-2204, No. 34,557-1.

[17] H. Gotthardt, J. Blum and K.-H. Schenk, *Chem. Ber.*, **119**, 1315 (1986).

[18a] M. E. Rogers, R. A. Glennon, J. D. Smith, M. R. Boots, N. Nanavati, J. E. Maconaughey, R. G. Bass and G. Mbagwu, *J. Med. Chem.*, **24**, 1284 (1981); [b] M. Hellberg, J. F. Stubbins and R. A. Glennon, *Bioorg. Med. Chem.*, **8**, 1917 (2000).

[19] For the N-unsubstituted 2-aminopyridine (which yields potentially tautomeric betaines) and further literature see: B. D. Schober and T. Kappe, *J. Heterocyclic Chem.*, **25**, 1231 (1988).

[20] R. A. Glennon, M. E. Rogers and M. K. El-Said, *J. Heterocyclic Chem.*, **17**, 337 (1980).

[21]W. Lube, Ph. D. Thesis, University of Graz, Austria, 1972.

[22] T. Kappe and R. Khorchid-Zadeh, *Synthesis*, 247 (1975).

[23]T. Kappe, Y. Ravai and W. Stadlbauer, *Monatsh. Chem.*, **114**, 227 (1983).

[24a] T. Kappe and W. Lube, *Chem. Ber.*, **112**, 3424 (1979); [b] K. T. Potts, R. Ehlinger and S. Kanemasa, *J. Org. Chem.*, **45**, 2474 (1980); [c] P. Roschger, Ph. D. Thesis, University of Graz, Austria (1990).

[25] C. Wentrup, W. Heilmayer and G. Kollenz, *Synthesis*, 1219 (1994), review.

[26a] H. Kraxner, Ph. D. Thesis, University of Graz, Austria (1982); [b] T. Kappe and C. Kos, *Synthesis*., 629 (1989); [c] A. Kutyrew and T. Kappe, *J. Heterocyclic Chem.*, **34**, 969 (1997).

[27] A. Kutyrew and T. Kappe, *J. Heterocyclic Chem.*, **36**, 237 (1999).

[28]E. M. Arnett, S. G. Maroldo, S. L. Schilling and J. A. Harrelson, *J. Am. Chem. Soc.*, **106**, 6759 (1984).

[29]J. Fuchs, K. F. Jahr and G. Heller, *Chem. Ber.*, **96**, 2472 (1963) and ref. given.

[30] A. F. McKay and M.-E. Kreling, C*anad. J. Chem.*, **40**, 1160 (1962).

[31] L. P. Hammett, Physikalische Chemie, Akademie-Verlag Chemie, Berlin, 1976, Chapter 9, pp. 263.

[32] K. Thonhofer, Ph. D. Thesis, University of Graz, Austria, 1977.

[33] H. Sterk, J. J. Suschnigg and K. Thonhofer, *Z. Naturforsch.*, **31A**, 793 (1976).