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New Fused Triazinium Systems from (Alkoxycarbonyl)azinium *N*-Aminides

Jesús Valenciano,[a] Esmeralda Sánchez-Pavón,[a][‡] Ana M. Cuadro,*[a] Julio Alvarez-Builla,[a] and Juan J. Vaquero*[a]

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2-(Alkoxycarbonyl)cycloimmonium *N*-aminides are efficient 1,4-dipoles that react with different types of reagents such as carbodiimides, benzoyliso(thio)cyanates and heterocyclic imidoyl chlorides to give new heterobetaines containing fused [1,2,4]triazinium systems.

Introduction

Heterocyclic mesomeric betaines[1] **1** are well established and versatile 1,3-dipoles, a characteristic that allows them to take part in 1,3-dipolar cycloaddition reactions.[2] They have also found widespread application in the synthesis of natural products and organic compounds of biological relevance.[3] 2-Alkyl- and 2-amino-substituted azinium salts **2** have the potential to function as 1,4-dinucleophiles by deprotonation and are capable (Figure 1) of reacting with dielectrophilic reagents such as 1,2-dicarbonyl compounds (Westphal reaction)[4] to give a variety of azonia derivatives incorporating quaternary bridgehead nitrogen systems.[5] In contrast, with the exception of only a few examples,[6] less attention has been paid to the possibility of using appropriately 1,2-substituted azinium salts **3** as synthetic equivalents of 1,4-nucleophilic/electrophilic ylides such as **4** (Figure 1). Except for isolated reports, the use of 1,4-dipole equivalents has generally remained underexploited.[7]

In connection with such compounds **3**, we previously reported the first example[8] of the behaviour of this system as a 1,4-nucleophile/electrophile through the intermediacy of *N*-aminides **4**. This behaviour was demonstrated through the reactivity of 2-(ethoxycarbonyl)azinium salts **3** with het-

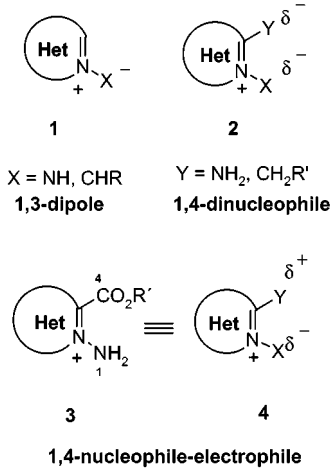
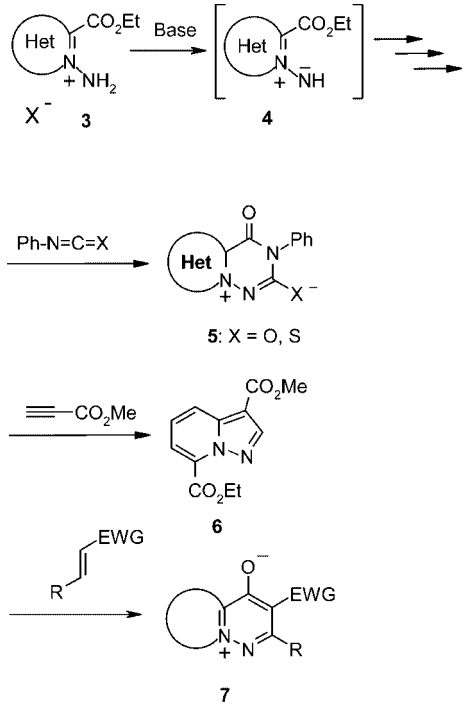


Figure 1. N-Ylides as 1,3-dipoles, 1,4-dinucleophiles, and 1,4-nucleophile/electrophile.



Scheme 1.

[a] Departamento de Química Orgánica, Universidad de Alcalá
28871 Alcalá de Henares, Madrid, Spain
E-mail: juanjose.vaquero@uah.es
ana.cuadro@uah.es
[‡] New address: Facultad de Ciencias Químicas, Universidad Veracruzana,
Apartado postal 215, Prolongación Oriente 6, N° 1009 CP 94340, Orizaba, Veracruz, Mexico

erocumulenes,[9] to afford heterobetaines **5**. We also found that the same *N*-aminides **4** can behave as 1,3-dipoles when they react with acetylenic and olefinic dipolarophiles to afford pyridopyrazoles **6** or heterobetaines **7** – in the latter case through a 1,3-cycloaddition reaction/ring expansion process[10] (Scheme 1).

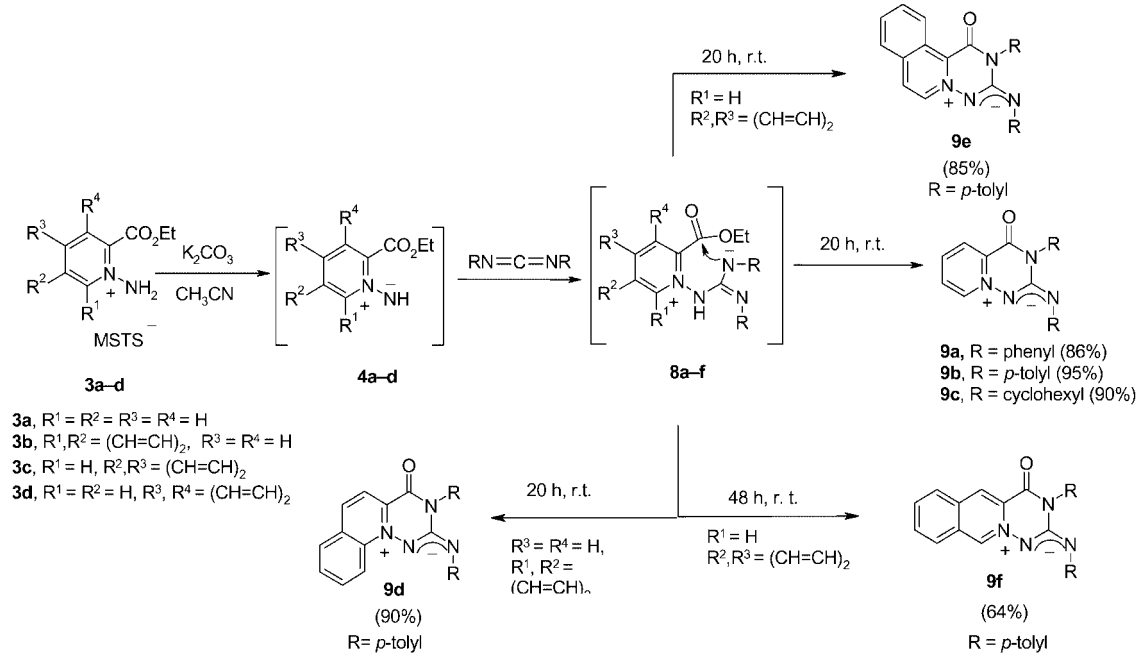
This interesting dual role found for (alkoxycarbonyl)cycloimmonium *N*-aminides **4** prompted us to carry out further studies in this area. The goal of this work was to gain a more detailed understanding of the reactivity of these azinium *N*-aminides as 1,4-dipole equivalents. Here we describe results relating to their reactivity with other heterocumulenes and heterocyclic imidoyl chlorides to provide new fused triazinium heterocyclic systems.

Results and Discussion

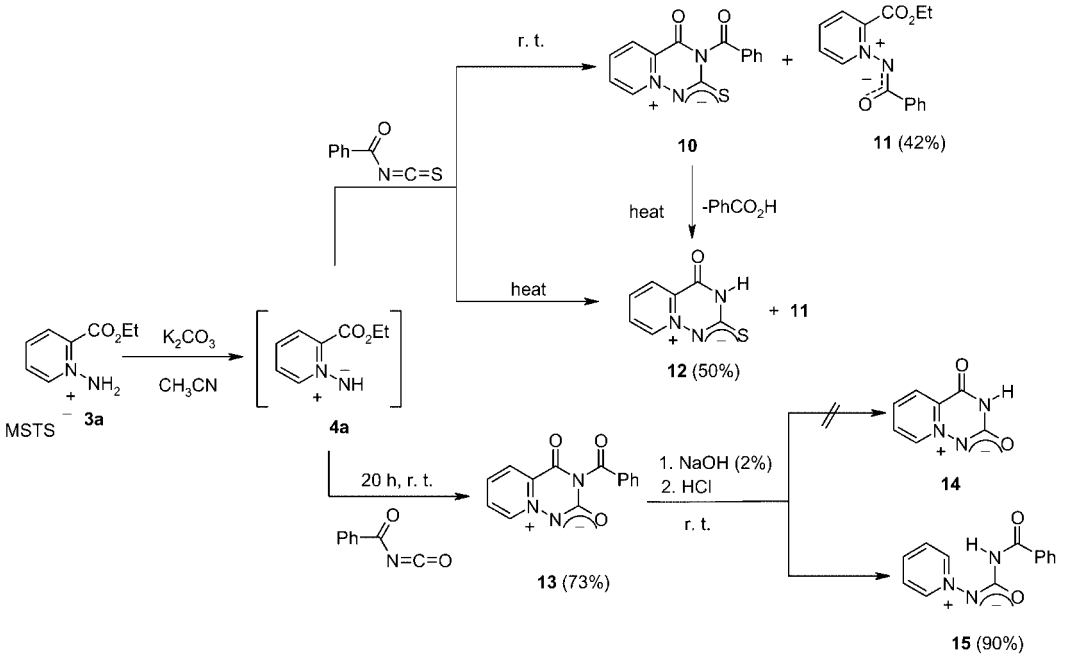
In the context of our ongoing investigations into the construction, via dipolar intermediates, of heterobetaines and in view of the behaviour of azinium *N*-aminides **4** described above, the precursor salts **3** were obtained by direct amination of the corresponding (alkoxycarbonyl)azines with use of mesitylenesulfonyl hydroxylamine (MSH) as the aminating agent (Scheme 2).[11] Under basic conditions (K_2CO_3/CH_3CN) these salts gave the corresponding 2-(alkoxycarbonyl)azinium *N*-aminides **4** (pyridinium, quinolinium, isoquinolinium), which were treated with cyclohexyl- and arylcarbodiimides to afford heterobetaines **9** in good yields. Reactions with diisopropylcarbodiimide were also attempted with salts **3a** and **3b**, but in these cases the corresponding cyclocondensation products were not detected. This result is probably due to steric interactions, which preclude the cyclization step. The formation of heterobetaines **9** can be envisaged as occurring via the corresponding dipolar intermediates **8**. Although these intermediates could not be detected in these reactions, we had previously described the isolation of similar intermediates and their transformation into the corresponding mesomeric betaines.[8]

The reaction between 2-(ethoxycarbonyl)pyridinium-*N*-aminide (**4a**), generated in a biphasic K_2CO_3/CH_3CN system, and benzoyl isothiocyanate at room temperature afforded a mixture of compounds that contained the heterobetaines **10** (38%) and **11** (42%). When this mixture was heated in CH_3CN or EtOH for 3 h, heterobetaine **10** was transformed into **12** through loss of the benzoyl moiety (Scheme 3). When the same reaction was carried out in CH_3CN at reflux, heterobetaine **12** was isolated in 50% yield along with **11**, which was formed in the same yield (42%) as when the reaction had been performed at room temperature. The aminide **11** was presumably formed as the result of an attack by the amino group in **4a** on the carbonyl group of the benzoyl isothiocyanate, followed by loss of isothiocyanic acid. The structure of **11** was easily confirmed by treatment of the *N*-aminide **4a** with benzoyl chloride.

Benzoyl isocyanate reacts with **4a** to give heterobetaine **13** as the main reaction product (73%) under the same conditions as used for the formation of **12** (Scheme 3). All attempts to transform **13** into the heterobetaine **14** by treatment with NaOH (2%) were unsuccessful and the only isolable compound was the pyridinium *N*-aminide **15** (90%). The formation of **15** can be explained in terms of ring-opening of the triazine ring through nucleophilic attack at the endocyclic carbonyl group and subsequent decarboxylation of the intermediate pyridinium carboxylate. ^{1}H NMR spectroscopy showed that this *N*-aminide was very unstable in solution.



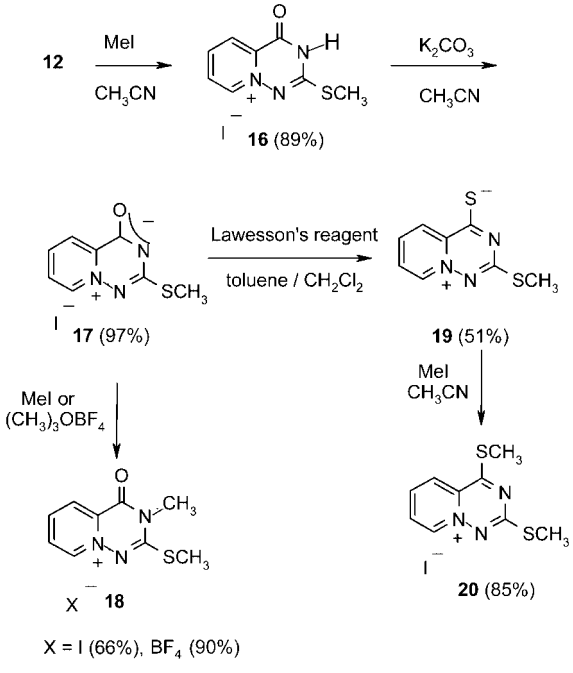
Scheme 2.



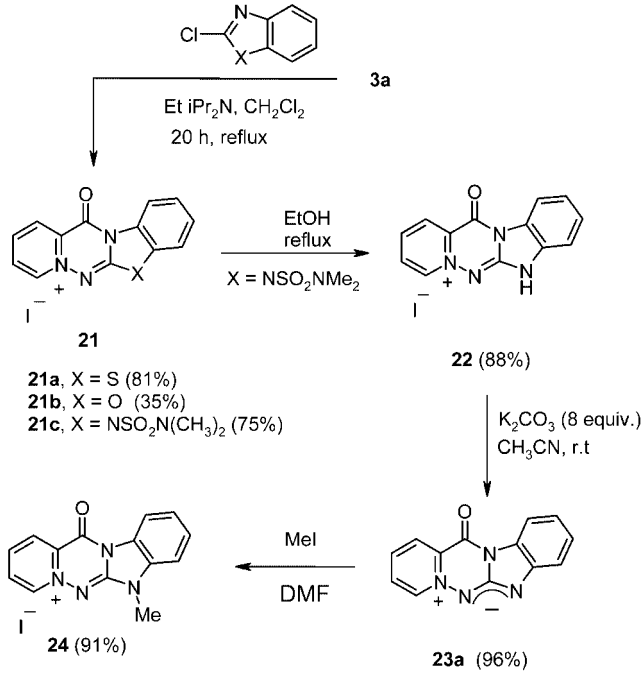
Scheme 3.

Compound **12** is an interesting heterobetaine with four potentially reactive nucleophilic sites on the triazine ring (oxygen, sulfur and two different nitrogens). Representative transformations of **12** into new benzotriazine derivatives through simple reactions are shown in Scheme 4. As one example, alkylation with methyl iodide is a very selective reaction that occurs only on the sulfur atom, with formation of the salt **16** in excellent yield. Treatment of **16** with K_2CO_3/CH_3CN provided the new mesomeric betaine **17** (97%), which gave **19** (51%) on treatment with Lawesson's reagent in boiling toluene or the salt **18**, in 66% or 90% yields, on treatment with methyl iodide or trimethyloxonium tetrafluoroborate, respectively.[6a,6b] Moreover, **19** reacted with methyl iodide at room temperature to give the 2,4-dimethylthiopyrido[2,1-*f*]triazinium iodide **20** in good yield (85%).

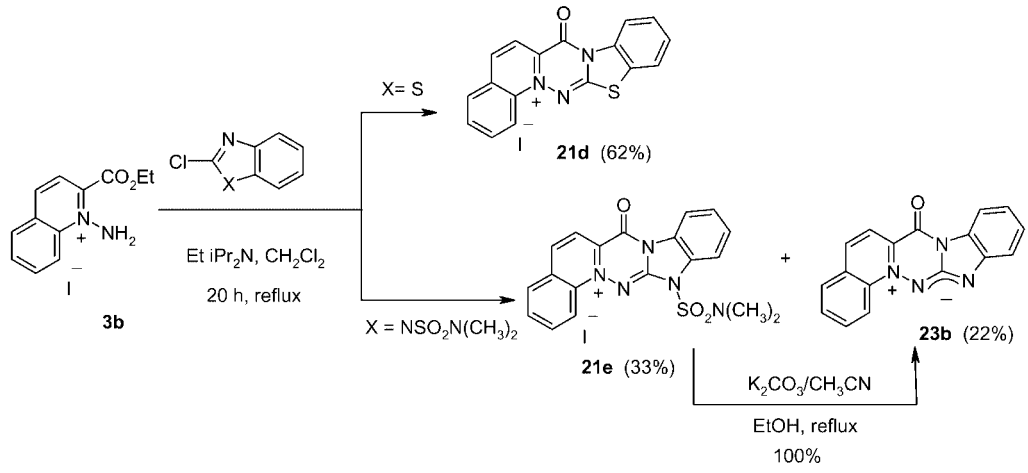
A new application of *N*-aminides as 1,4-dipoles with different heterocyclic imidoyl chlorides (Scheme 5) as reactive



Scheme 4.



Scheme 5.



Scheme 6.

nucleophilic/electrophilic partners was also studied.[10] Initial examination of the reactivity of **3a** with 2-chlorobenzothiazole in a biphasic system (anhydrous K_2CO_3 and dry CH_3CN), followed by stirring at room temperature for 6 h, afforded **21a** in modest yield (40%). Better results (60%) were obtained with use of salt **3a** as the iodide, probably because **21a** as the iodide precipitates in the homogeneous reaction medium in the presence of *N*,*N*-diisopropylethylamine (Hünig's base) in CH_2Cl_2 (room temperature, 20 h). Finally, the best yield was obtained by heating the reaction mixture at reflux overnight (81%). When these conditions were applied to 2-chlorobenzoxazole, the corresponding tetracyclic triazine **21b** was obtained – albeit in only 24% yield. Different reaction conditions were tested to improve this yield, with the best results (35% yield) being obtained with CH_3CN as the solvent. This low yield is probably due to a nucleophilic attack at the C-6a position followed by a ring-opening reaction of the benzoxazole ring.

Unprotected and *N*-benzyl-protected 2-chlorobenzimidazoles did not react with **3a** either under biphasic or under homogeneous conditions, but high yields (75%) of the pyridotriazinobenzimidazolium compound **21c** were obtained when the **3a** was used as its sulfamoyl derivative (Scheme 5). The protecting group can be removed from **21c** under mild neutral reaction conditions (EtOH reflux, 6 h) to furnish **22** in 88% yield. Treatment of **22** with K_2CO_3 in CH_3CN generated the heterobetaine **23a**, which was selectively *N*-methylated with MeI/DMF to give **24** in 91% yield (Scheme 5).

The *N*-aminide generated from **3b** also reacted with 2-chlorobenzothiazole in CH_2Cl_2 to give **21d** in 62% yield and with the *N*-sulfamoyl-protected 2-chlorobenzimidazole to afford a mixture of the benzimidazotriazinoquinolinium salt **21e** (33%) and the heterobetaine **23b** (22%). Quantitative conversion of **21e** into **23b** was achieved by heating **21e** at reflux in EtOH (Scheme 6).

Conclusions

In conclusion, the results described here illustrate further applications of the synthetic utility of *N*-aminides **4** as 1,4-nucleophilic/electrophilic reagents. This behaviour allowed a straightforward synthesis of new pyrido[2,1-*f*][1,2,4]triazinium salts, which can be regarded as suitable precursors for new charged guanidine derivatives through ring-opening reactions.

Experimental Section

General Remarks: Melting points were determined on an Electrothermal IA9100 apparatus. Infrared spectra were recorded on a Perkin–Elmer 1310 spectrophotometer with use of KBr pellets, and bands are reported in cm^{-1}. The ^1H and ^{13}C NMR spectra were recorded on Varian Unity instruments (200, 300 and 50 MHz). Chemical shifts are reported as δ values (ppm). Mass spectra were determined on a Hewlett–Packard 5988A (70 eV) spectrometer. Column chromatography was performed on silica gel (Merck 60, 0.040–0.063 mm). Mesitylenesulfonate of azinium salts **3** were obtained by previously described methods.[8,10a,11] The starting azinium salts were obtained as iodides by stirring of the corresponding mesitylenesulfonates with HI (57%. 1.5 equiv.) in EtOAc. All other chemicals are commercially available.

Treatment of Salts 3 with Carbodiimides. General Procedure for the Preparation of Heterobetaines 9: The appropriate carbodiimide (1.1 mmol) was added to a stirred suspension of azinium salt **3** (1 mmol) and anhydrous K_2CO_3 (0.55 g, 4 mmol) in dry acetonitrile (10 mL). The mixture was stirred at room temperature for 20 h and the inorganic residue was filtered off. The organic phase was concentrated and extracted with toluene (3 × 10 mL), reconcentrated and recrystallized from the appropriate solvent.

3-Phenyl-4-oxo-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium-2-(*N*′-phenyl)aminide[12] **(9a):** This compound was prepared from **3a** and *N*,*N*′-diphenylcarbodiimide by the General Procedure. Purification gave **9a** (0.26 g, 85%) as a red solid: m.p. 128–129 °C (Et_2O). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.28–8.22 (m, 1 H), 8.09 (d, *J* = 6.6 Hz, 1 H,), 7.55–7.48 (m, 2 H), 7.46–7.35 (m, 5 H), 7.25–7.16 (m, 2 H), 7.02–6.97 (m, 2 H), 6.95–6.88 (m, 1 H) ppm.). IR (KBr): $\tilde{\nu}$ = 1691, 1564, 1493, 1439, 1399, 1189, 1146 cm^{-1}. MS (*m*/*z*): 314 $[M]^+$ (10), 287 (16), 194 (100). $C_{19}H_{14}N_4O$ (314.35): calcd. C 72.60, H 4.49, N, 17.82; found: C 72.47, H, 4.79, N, 17.35.

4-Oxo-3-*p*-tolyl-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium-2-(*N*′-*p*-tolyl)aminide (9b): The above procedure was used with **3a** and di-*p*-tolylcarbodiimide, to provide **9b** (0.33 g, 95%) as a dark red solid: m.p. 207–208 °C (toluene). ^1H NMR ($[D_6]$DMSO, 300 MHz): δ =

8.27 (d, J = 6.3 Hz, 1 H), 8.11 (dd, J_1 = 8.5, J_2 = 2 Hz, 1 H), 7.73–7.65 (m, 1 H), 7.63–7.57 (m, 1 H), 7.25 (d, J = 8.4 Hz, 2 H), 7.18 (d, J = 8.4 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2 H), 6.74 (d, J = 8.4 Hz, 2 H), 2.34 (s, 3 H), 2.17 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.3, 148,1 146.4, 138.1, 133.6, 133.1, 132.1, 130.8, 130.1, 128.8, 128.6, 127.8, 127.1, 126.4, 122.9, 21.3, 20.9 ppm. IR (KBr): $\tilde{\nu}$ = 1686, 1611, 1567, 1505, 1436, 1394, 1190, 1138 cm^{-1}. MS (*m*/*z*): 343 $[M + 1]^+$ (100). $C_{21}H_{18}N_4O$ (342.40): calcd. C 73.66, H 5.30, N 16.36; found: C 73.72, H 5.44, N, 16.15.

3-Cyclohexyl-4-oxo-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium-2-(*N*′-cyclohexyl)aminide (9c): The General Procedure was used with **3a** and *N*,*N*′-dicyclohexylcarbodiimide, to provide **9c** as an orange solid (0.29 g, 90%): m.p. 133–134 °C (pentane/hexane). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.16 (d, J = 6.2 Hz, 1 H), 7.96 (dd, J_1 = 8.0, J_2 = 2.3 Hz, 1 H), 7.59–7.53 (m, 1 H), 7.43–7.36 (m, 1 H), 5.08–4.95 (m, 1 H), 3.75–3.60 (m, 1 H), 2.52–2.48 (m, 2 H), 1.80–1.00 (m, 18 H) ppm. IR (KBr): $\tilde{\nu}$ = 2927, 1675, 1595, 1444, 1228, 1186 cm^{-1}. $C_{19}H_{26}N_4O$ (326.45): calcd. C 69.91, H 8.03, N 17.16; found: C 69.80, H 8.25, N, 17.27.

4-Oxo-3-*p*-tolyl-3,4-dihydro[1,2,4]triazino[1,6-*a*]quinolin-11-ium-2-(*N*′-*p*-tolyl)aminide (9d): This compound was prepared from **3b** and *N*,*N*′-di-*p*-tolylcarbodiimide by the General Procedure. Purification gave **9d** (0.35 g, 90%) as a violet-blue solid: mp 185–187 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.75–8.70 (m, 1 H), 8.16 (d, J = 8.4 Hz, 1 H), 7.87–7.82 (m, 1 H), 7.78–7.70 (m, 3 H), 7.36–7.28 (m, 4 H), 7.12–7.03 (m, 4 H), 2.41 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 157.2, 148.0, 146.5, 138.2, 135.6, 133.1, 131.7, 131.1, 130.8, 130.7, 130.2, 129.1, 128.8, 128.3, 127.8, 126.6, 123.1, 120.7, 119.7, 21.3, 21.0 ppm. IR (KBr): $\tilde{\nu}$ = 1679, 1558, 1504, 1461, 1413, 1185, 1145 cm^{-1}. MS (*m*/*z*): 391 $[M - 1]^+$ (87), 392 $[M]^+$ (44). $C_{25}H_{20}N_4O$ (392.46): C 76.51, H 5.14, N 14.28; found: C 76.13, H 5.29, N 13.90.

4-Oxo-3-*p*-tolyl-3,4-dihydro[1,2,4]triazino[1,6-*a*]isoquinolin-5-ium-2-(*N*′-*p*-tolyl)aminide (9e): This compound was prepared from **3c** and *N*,*N*′-di-*p*-tolylcarbodiimide by the General Procedure, giving **9e** (0.33 g, 85%) as a red crystalline solid: m.p. 248–249 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.64 (d, J = 8.4 Hz, 1 H), 7.98 (d, J = 7.3 Hz, 1 H), 7.75–7.58 (m, 4 H), 7.38–7.27 (m, 4 H), 7.05–6.92 (m, 4 H), 2.41 (s, 3 H), 2.28 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1679, 1574, 1499, 1458, 1442, 1142 cm^{-1}. MS (*m*/*z*): 343 $[M + 1]^+$ (100). $C_{25}H_{20}N_4O$ (392.46): calcd. C 76.51, H 5.14, N 14.28; found: C 76.82, H 5.33, N 13.90.

4-Oxo-3-*p*-tolyl-3,4-dihydro[1,2,4]triazino[1,6-*b*]isoquinolin-11-ium-2-(*N*′-*p*-tolyl)aminide (9f): Use of **3d** and *N*,*N*′-di-*p*-tolylcarbodiimide and stirring of the reaction mixture for 5 d gave **9f** (0.25 g, 64%) as a dark red solid: m.p. 220–221 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.74 (s, 1 H), 8.71 (s, 1 H), 7.91 (d, J = 8.1 Hz, 1 H), 7.68–7.60 (m, 3 H), 7.35–7.24 (m, 4 H), 7.08 (d, J = 8.4 Hz, 2 H), 6.94 (d, J = 8.4 Hz, 2 H), 2.40 (s, 3 H), 2.28 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1678, 1627, 1584, 1505, 1439, 1407, 1312, 1160 cm^{-1}. $C_{25}H_{20}N_4O$ (392.46): calcd. C 76.51, H 5.14, N 14.28; found: C 76.45, H 5.01, N, 14.22.

Reactions between the Salt 3a and Benzoyl Iso(thio)cyanates

4-Oxo-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium-2-thiolate (12): A stirred suspension of **3a** (0.37 g, 1 mmol) in dry acetonitrile (10 mL), benzoyl isothiocyanate (0.15 mL, 1.1 mmol) and anhydrous K_2CO_3 (0.55 g, 4 mmol) were mixed under argon. The reaction mixture was stirred at room temperature for 20 h, and the filtrate was collected and concentrated under reduced pressure to afford **10**. Further heating of **10** at reflux in EtOH for 3 h gave **12** (90 mg, 50%) as a yellow solid: m.p. 236–237 °C (EtOH). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 12.47 (1 H, –NH), 8.78 (d, J = 6.2 Hz, 1 H), 8.33 (dd, J_1 = 7.9, J_2 = 1.7 Hz, 1 H), 8.16–8.06 (m, 1 H), 8.06–7.96 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 175.3, 154.2, 136.7, 136.6, 135.8, 129.9, 125.0 ppm. IR (KBr): $\tilde{\nu}$ = 3054, 1687, 1613, 1510, 1472, 1400, 1175, 1139 cm^{-1}. MS (*m*/*z*): 179 $[M]^+$ (22), 147 (7), 106 (51), 78 (100). $C_7H_5N_3OS$ (179.20): calcd. C 46.92, H 2.81, N 23.45; found: C 46.54, H 2.94, N 23.20.

2-(Ethoxycarbonyl)pyridinium-*N*-(*N*′-benzoyl)aminide (11): This compound was isolated by column chromatography (silica gel) with acetone/MeOH (9:1) as eluent, to give **11** (0.069 g, 42%) as a yellow oil. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.04 (d, J = 6.6 Hz, 1 H), 8.26 (td, J_1 = 7.8, J_2 = 1.1 Hz, 1 H), 8.13 (dd, J_1 = 7.8, J_2 = 1.8 Hz, 1 H), 8.04–7.92 (m, 3 H), 7.46–7.32 (m, 3 H) ppm. MS (*m*/*z*): 197 $[M - CO_2Et]^+$ (100), 156 (13), 105(99), 77(78).

3-Benzoyl-4-oxo-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium-2-olate (13): Anhydrous K_2CO_3 (0.55 g, 4 mmol) was added to a solution of **3a** (0.37 g, 1 mmol) and benzoyl isocyanate (0.14 mL, 1.1 mmol) in dry acetonitrile (10 mL). The suspension was stirred for 20 h at room temperature, the solvent was removed, and the residue was triturated with water (10 mL). The precipitate was filtered, washed with water until neutral and recrystallized from EtOH to give **13** (0.20 g, 73%) as white needles: m.p. 208–209 °C (EtOH). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 8.80–8.70 (m, 1 H), 8.40–8.30 (m, 1 H), 8.18–8.08 (m, 2 H), 8.05–7.95 (m, 2 H), 7.82–7.70 (m, 1 H), 7.63–7.50 (m, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 171.1, 169.8, 156.4, 137.4, 136.7, 135.3, 134.0, 131.4, 130.6, 130.0, 129.2, 125.5 ppm. IR (KBr): $\tilde{\nu}$ = 1746, 1692, 1626, 1445, 1392, 1232, 1193 cm^{-1}. $C_{14}H_9N_3O_3$ (267.25): calcd. C 62.92, 3.39, N 15.72; found: C 62.56, H 3.53, N 15.83.

Pyridinium *N*-(*N*′-Benzoylaminocarbonyl)aminide (15): A solution of **13** (29 mg, 0.075 mmol) in NaOH (2%, 2 mL) was stirred at room temperature for 2 h and then treated with HCl (2%). After evaporation of the solvent, the residue was treated with EtOH, to give **15** (16 mg, 90%) as a pale yellow solid that was very unstable. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.40–10.00 (br s, 1 H), 8.87–8.80 (m, 2 H), 8.30–8.20 (m, 1 H), 8.02–7.85 (m, 2 H), 7.88 (d, J = 7.4 Hz, 2 H), 7.60–7.40 (m, 3 H) ppm.

Synthesis of Heterobetaines 16–20

2-Methylthio-4-oxo-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium Iodide (16): Methyl iodide (0.25 mL, 4 mmol) was added to a suspension of **12** (0.09 g, 0.5 mmol) in dry acetonitrile (5 mL). The mixture was stirred for 20 h at room temperature and the precipitate was isolated by filtration to yield **16** (0.14 g, 89%) as a yellow solid: m.p. 209–210 °C. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.19 (d, J = 6.2 Hz, 1 H), 8.65–8.50 (m, 2 H), 8.35–8.26 (m, 1 H), 2.61 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 2830, 1724, 1582, 1551, 1456, 1438 cm^{-1}. $C_8H_8IN_3OS$ (194.12): calcd. C 9.92, H 2.51, N 13.08; found: C 9.89, H 2.53, N 13.27.

2-Methylthiopyrido[2,1-*f*][1,2,4]triazin-9-ium-4-olate (17): Anhydrous K_2CO_3 (0.28 g, 2 mmol) was added to a suspension of **16** (0.16 g, 0.5 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 20 h and concentrated to dryness, and the residue was purified by column chromatography (silica gel) with acetone as eluent, to give **17** (0.094 g, 97%) as a white solid: m.p. 189–190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.66 (dd, J_1 = 8.0, J_2 = 1.4 Hz, 1 H), 8.58 (d, J = 6.6 Hz, 1 H), 8.10–8.02 (m, 1 H), 7.86–7.78 (m, 1 H), 2.57 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1638, 1605, 1500, 1440, 1368, 1223 cm^{-1}. $C_8H_7N_3OS$ (193.23): calcd. C 49.72, H 3.65; N 21.75; found: C 49.91, H, 3.91, N 21.51.

3-Methyl-2-methylthio-4-oxo-3,4-dihydropyrido[2,1-*f*][1,2,4]triazin-9-ium Iodide (18): Methyl iodide (0.25 mL, 4 mmol) was added to

a suspension of **17** (0. 096 g, 0.5 mmol) in dry acetonitrile (5 mL). The mixture was stirred for 48 h at room temperature and the precipitate was isolated by filtration to yield **18** (0.11 g, 66%) as a yellow solid: m.p. 248–249 °C (EtOH). ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.33 (d, J = 5.9 Hz, 1 H), 8.75 (dd, J_1 = 8.1, J_2 = 1.8 Hz, 1 H), 8.70–8.60 (m, 1 H), 8.47–8.37 (m, 1 H), 3.54 (s, 3 H), 2.74 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1706, 1580, 1545, 1470, 1443, 1404, 1344, 1118 cm^{-1}. $C_9H_{10}IN_3OS$ (208.27): calcd. C 32.25, H 3.01, N 12.54; found: C 31.93, H 2.91, N 12.15.

2-Methylthiopyrido[2,1-*f*][1,2,4]triazin-9-ium-4-thiolate (19): A suspension of **17** (0.097 g, 0.5 mmol) and Lawesson reagent (0.15 g, 0.38 mmol) in CH_2Cl_2/toluene (1:1, 10 mL) was heated at reflux for 20 h. After this time, the reaction mixture was concentrated to dryness and the residue was purified by column chromatography (silica gel) with dichloromethane/acetone (9:1) as eluent, to give **19** as an orange solid (0.053 g, 51%): m.p 216–217 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.30 (dd, J_1 = 8.4, J_2 = 1.4 Hz, 1 H), 8.52 (d, J = 6.2 Hz, 1 H), 8.10–8.02 (m, 1 H), 7.86–7.78 (m, 1 H), 2.59 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1450, 1423, 1354, 1250, 1202 cm^{-1}. $C_8H_7N_3S_2$ (209.29): calcd. C 45.91, H 3.37, N 20.08; found: C 45.54, H 3.62, N 19.70.

2,4-Dimethylthiopyrido[2,1-*f*][1,2,4]triazin-9-ium Iodide (20): A mixture of **19** (0.021 g, 0.1 mmol) and methyl iodide (0.05 mL, 0.8 mmol) in ethyl acetate (5 mL) was stirred at room temperature for 20 h. The precipitate was then isolated by filtration to afford **20** (0.030 g, 85%) as a yellow solid: m.p. 223–224 °C. ^{1}H NMR ([D$_6$]-DMSO, 300 MHz): δ = 9.47 (d, J = 6.2 Hz, 1 H), 8.81 (d, J = 7.8 Hz, 1 H), 8.72–8.62 (m, 1 H), 8.50–8.40 (m, 1 H), 2.80 (s, 3 H), 2.71 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 3422, 1526, 1480, 1294, 1210 cm^{-1}. $C_9H_{10}IN_3S_2$ (224.33): calcd. C 30.78, H 2.87, N 11.96; found: C 30.91, H 3.10, N 11.58.

Reactions between the Salts 3 and Heterocyclic Imidoyl Chlorides. General Procedure: *N*,*N*-Diisopropylethylamine (0.35 mL, 2 mmol) was added dropwise to a solution of an azinium salt **3** as an iodide (1 mmol) and the corresponding heterocyclic imidoyl chloride (1.1 mmol) in dry CH_2Cl_2 (10 mL). The mixture was heated under reflux for 20 h. The resulting precipitate was removed by filtration, washed with CH_2Cl_2 and recrystallized from the appropriate solvent.

12-Oxo-12,13-dihydropyrido[1′,2′:1,6][1,2,4]triazino[3,4-*b*]benzothiazol-7-ium Iodide (21a): By use of the General Procedure, with 1-amino-2-(ethoxycarbonyl)pyridinium iodide **3a** (0.29 g, 1 mmol) and 2-chlorobenzothiazole (0.19 g, 1.1 mmol), **21a** (0.31 g, 81%) was isolated as a yellow solid: m.p. >300 °C (MeOH). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 9.53 (d, J = 5.9 Hz, 1 H), 9.05 (dd, J_1 = 8.0, J_2 = 1.5 Hz, 1 H), 8.86–8.68 (m, 2 H), 8.60–8.48 (m, 1 H), 8.32–8.20 (m, 1 H), 7.84–7.64 (m, 2 H) ppm. ^{13}C ([D$_6$]DMSO, 50 MHz): δ = 162.0, 152.4, 142.8, 140.3, 134.9, 133.9, 131.4, 128.8, 128.5, 126.1, 124.3, 122.7, 118.1 ppm. IR (KBr): $\tilde{\nu}$ = 1724, 1580, 1548, 1478, 1438, 1340 cm^{-1}. $C_{13}H_8IN_3OS$ (254.29): calcd. C 40.96, H 2.12 N, 11.02; found: C 40.76, H 2.16, N 10.91.

12-Oxo-12,13-dihydropyrido[1′,2′:1,6][1,2,4]triazino[3,4-*b*]benzoxazol-7-ium Iodide (21b): A mixture of **3a** (0.29 g, 1 mmol) and 2-chlorobenzoxazole (0.17 g, 1.1 mmol) was heated at reflux for 4 h in dry acetonitrile, affording **21b** (0.13 g, 35%) as a yellow solid: m.p. >300 °C. ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 9.65 (d, J = 6.3 Hz, 1 H), 9.08 (dd, J_1 = 8.1, J_2 = 1.7 Hz, 1 H), 8.88–8.76 (m, 1 H), 8.65–8.54 (m, 1 H), 8.35–8.26 (m, 1 H), 8.08–8.00 (m, 1 H), 7.82–7.64 (m, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 155.2, 151.1, 144.2, 143.4, 142.2, 135.0, 132.0, 129.3, 127.2, 126.6, 124.1, 115.4, 112.4 ppm. IR (KBr): $\tilde{\nu}$ = 1728, 1670, 1622, 1482, 1404 cm^{-1}. $C_{13}H_8IN_3O_2$ (238.23): calcd. C 42.76, H 2.21, N 11.51; found: C 42.72, H 2.33, N 11.78.

7-(*N*,*N*′-Dimethylsulfamoyl)-13-oxo-12,13-dihydro-7*H*-pyrido[1′,2′:-1,6][1,2,4]triazino[4,3-*a*]benzimidazol-5-ium Iodide (21c): By use of the General Procedure with **3a** (0.29 g, 1 mmol) and 2-chloro-1-(*N*,*N*-dimethylsulfamoyl)benzimidazole (0.29 g, 1.1 mmol), **21c** was isolated as a yellow solid (0.35 g, 75%): m.p. 174–175 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 9.60 (d, J = 6.0 Hz, 1 H), 9.05 (dd, J_1 = 8.0, J_2 = 1.6 Hz, 1 H), 8.73 (td, J_1 = 7.8, J_2 = 1.0 Hz, 1 H), 8.58–8.48 (m, 2 H), 8.13–8.03 (m, 1 H), 7.80–7.60 (m, 2 H), 3.16 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1724, 1638, 1484, 1442, 1398, 1288, 1266, 1182 cm^{-1}. $C_{15}H_{14}IN_5O_3$ (344.37): calcd. C 38.23, H 2.99, N 14.86; found: C 38.27, H 3.06, N 14.94.

7-Oxo-7,8-dihydrobenzothiazo[2′,3′:3,4]triazino[1,6-*a*]quinolin-15-ium Iodide (21d): By use of the General Procedure with 1-amino-2-(ethoxycarbonyl)quinolinium iodide **3b** (0.34 g, 1 mmol) and 2-chlorobenzothiazole (0.19 g, 1.1 mmol), **21d** (0.27 g, 62%) was obtained as a brown solid: m.p. 282–283 °C (MeOH). ^{1}H NMR ([D$_6$]-DMSO, 200 MHz): δ = 9.35 (d, J = 8.8 Hz, 1 H), 9.27 (d, J = 8.8 Hz, 1 H), 8.98 (d, J = 8.8 Hz, 1 H), 8.88–8.82 (m, 1 H), 8.68–8.62 (m, 1 H), 8.47–8.20 (m, 3 H), 7.84–7.76 (m, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 161.2, 152.8, 142.8, 136.5, 135.3, 135.1, 133.8, 132.5, 130.4, 130.3, 129.1, 128.7, 124.4; 123.5, 119.1, 118.7, 118.4 ppm. IR (KBr): $\tilde{\nu}$ = 1720, 1586, 1553, 1515, 1373, 1334, 1240, 1219 cm^{-1}. $C_{17}H_{10}IN_3OS$ (304.45): calcd. C 47.35, H 2.34, N 9.74; found: C 47.35, H 2.45, N 9.82.

13-(*N*,*N*′-Dimethylsulfamoyl)-7-oxo-7,8-dihydro-13*H*-benzimidazo-[2′,1′:3,4][1,2,4]triazino[1,6-*a*]quinolin-15-ium Iodide (21e) and the Heterobetaine 23b: By use of the General Procedure with 1-amino-2-(ethoxycarbonyl)quinolinium iodide **3b** (0.34 g, 1 mmol) and 2-chloro-1-(*N*,*N*-dimethylsulfamoyl)benzimidazole (0.29 g, 1.1 mmol), compound **21e** (0.17 g, 33%) was obtained as an orange solid: m.p. 191–192 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 9.32 (d, J = 8.8 Hz, 1 H), 9.16 (d, J = 8.8 Hz, 1 H), 8.98 (d, J = 8.8 Hz, 1 H), 8.70–8.42 (m, 3 H), 8.33–8.10 (m, 2 H), 7.90–7.66 (m, 2 H), 3.17 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1717, 1633, 1564, 1398, 1180 cm^{-1}. $C_{19}H_{16}IN_5O_3S$ (394.44): calcd. C 43.77, H 3.09, N, 13.43; found: C 43.93, H 3.13, N 13.62.

The filtrate was concentrated to dryness and chromatographed (silica gel), with EtOAc/acetone (8:2) as eluent, yielding **23b** (63 mg, 22%) as a dark red solid: m.p. 255–256 °C. IR (KBr): $\tilde{\nu}$ = 3416, 1684, 1612, 1540, 1441, 1184 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.45 (d, J = 9.0 Hz, 1 H), 8.62 (d, J = 8.0 Hz, 1 H), 8.56 (d, J = 9.0 Hz, 1 H), 8.04–7.94 (m, 3 H), 7.92–7.84 (m, 2 H), 7.66–7.58 (m, 1 H); 7.46–7.39 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 153.1, 150.7, 145.5, 136.7, 131.9, 130.8, 130.0, 128.6, 127.4, 127.3, 127.1, 126.3, 121.8, 120.7, 119.6, 118.4, 115.9 ppm. $C_{17}H_{10}N_4O$ (286.30): calcd. C 71.32, H 3.52, N 19.57; found: C 71.07, H 3.45, N 19.42.

13-Oxo-12,13-dihydro-7*H*-pyrido[1′,2′:1,6][1,2,4]triazino[4,3-*a*]-benzimidazol-5-ium Iodide (22): A suspension of **21c** (0.24 g, 0.5 mmol) in EtOH (10 mL) was heated at reflux for 24 h. The solution was concentrated and the resulting precipitate was filtered off, yielding **22** (0.16 g, 88%) as an orange solid: m.p. 299–300 °C (EtOH). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 9.33–9.26 (m, 1 H), 8.84 (dd, J_1 = 7.8, J_2 = 2.0 Hz, 1 H), 8.44–8.22 (m, 3 H), 7.70–7.55 (m, 2 H), 7.45 (ddd, J_1 = 7.0, J_2 = 6.0, J_3 = 2.3 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 152.1, 148.4, 139.2, 137.9, 133.7, 131.6, 130.5, 128.4, 126.0, 125.0, 123.6, 115.5, 112.5 ppm. IR (KBr): $\tilde{\nu}$ = 1716, 1636, 1480, 1438, 1196 cm^{-1}. $C_{13}H_9IN_4O$ (237.24): calcd. C 42.88, H 2.49, N 15.39; found: C 42.73, H 2.15, N 15.29.

Heterobetaine 23a: A suspension of **22** (0.18 g, 0.5 mmol) and K_2CO_3 (0.55 g, 4 mmol) in dry acetonitrile (5 mL) was stirred at room temperature for 6 h. The reaction mixture was filtered off and washed with water until neutral and then with acetonitrile, yielding **23a** (0.11 g, 96%) as dark orange solid. m.p. >300 °C (DMF). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 8.98 (d, J = 6.4 Hz, 1 H), 8.58 (dd, J_1 = 7.9, J_2 = 1.8 Hz, 1 H), 8.36 (d, 7.8 Hz, 1 H), 8.06–7.80 (m, 2 H), 7.62 (d, J = 8.2 Hz, 1 H), 7.50–7.42 (m, 1 H), 7.30–7.20 (m, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 1680, 1618, 1546, 1196 cm^{-1}. $C_{13}H_8N_4O$ (236.23): calcd. C 66.10, H 3.41, N 23.72; found: C 65.98, H 3.37, N 23.50.

7-Methyl-13-oxo-12,13-dihydro-7*H*-pyrido[1′,2′:1,6][1,2,4]triazino-[4,3-*a*]benzimidazol-5-ium Iodide (24): A suspension of **23a** (24 mg, 0.1 mmol) and methyl iodide (0.4 mmol, 25 μL) in DMF (2 mL) was stirred at room temperature for 6 h. EtOAc (5 mL) was then added and the precipitate was isolated by filtration and washed with EtOAc to afford **24** (34 mg, 91%) as a yellow solid: m.p. > 300 °C (DMF). ^{1}H NMR ([D$_6$]DMSO, 200 MHz): δ = 9.43 (d, J = 6.4 Hz, 1 H), 8.95 (dd, J_1 = 8.1, J_2 = 1.8 Hz, 1 H), 8.55 (td, J_1 = 7.8, J_2 = 1.2 Hz, 1 H), 8.47–8.37 (m, 2 H), 7.90 (d, J = 8.3 Hz, 1 H), 7.80–7.68 (m, 1 H), 7.66–7.52 (m, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 50 MHz): δ = 151.7, 147.0, 139.7, 139.0, 133.8, 131.7, 130.8, 128.3, 126.1, 124.4, 123.9, 115.3, 111.0, 29.1 ppm. IR (KBr): $\tilde{\nu}$ = 1724, 1636, 1482, 1440, 1188 cm^{-1}. $C_{14}H_{11}IN_4O$ (251.27): calcd. C 44.47, H 2.39, N 14.82; found: C 44.16, H 2.25, N 14.53.

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[1] W. D. Ollis, S. P. Stanforth, C. A. Ramsden, *Tetrahedron* **1985**, *41*, 2239–2329.

[2] a) A. Padwa, in: *1,3-Dipolar Cycloaddition Chemistry*, vol. 2 (Eds.: E. C. Taylor, A. Weissberger), John Wiley, New York, **1984**.

[3] a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), John Wiley & Sons, New York, **2002**; b) M. F. Liu, Y. Cheng, *Chem. Commun.* **2006**, 1215–1217.

[4] O. Westphal, K. Jahn, W. E. Heffe, *Arch. Pharm.* **1961**, *294*, 37–45.

[5] For some contributions, see: a) A. Molina, J. J. Vaquero, J. L. García-Navío, J. Alvarez-Builla, M. M. Rodrigo, O. Castaño, J. L. de Andrés, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1453–1456; b) J. Pastor, J. Siro, J. L. García-Navio, J. J. Vaquero, M. M. Rodrigo, M. Ballesteros, J. Alvarez-Builla, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3043–3048; c) J. Pastor, J. G. Siro, J. L. García-Navío, J. J. Vaquero, J. Alvarez-Builla, F. Gago, B. de Pascual-Teresa, M. Pastor, M. Rodrigo, *J. Org. Chem.* **1997**, *62*, 5476–5483; d) A. Molina, J. J. Vaquero, J. L. García-Navío, J. Alvarez-Builla, B. de Pascual-Teresa, F. Gago, M. M. Rodrigo, *J. Org. Chem.* **1999**, *64*, 3907–3915; e) V. Martinez, C. Burgos, J. Alvarez-Builla, G. Fernandez, A. Domingo, R. García-Nieto, F. Gago, I. Manzanares, C. Cuevas, J. J. Vaquero, *J. Med. Chem.* **2004**, *47*, 1136–1148.

[6] a) S. Bátori, Zs. Juhász-Riedl, P. Sandor, A. Messmer, *J. Heterocycl. Chem.* **1986**, *23*, 375–380; b) ,S. Bátori, A. Messmer, *J. Heterocycl. Chem.* **1988**, *25*, 437–444; c) S. Bátori, G. Hajós, P. Sándor, A. Messmer, *J. Org. Chem.* **1989**, *54*, 3062–3068; d) S. Bátori, A. Messmer, *J. Heterocycl. Chem.* **1990**, *27*, 1673–1680.

[7] For reports on 1,4-dipole equivalents, see: a) V. Nair, A. R. Sreekanth, A. T. Biju, N. P. Rath, *Tetrahedron Lett.* **2003**, *44*, 729–732; b) V. Nair, A. R. Sreekanth, N. Abhilash, M. M. Bhadbhade, R. C. Gonnade, *Org. Lett.* **2002**, *4*, 3575–3577; c) I. Ungureanu, P. Klotz, A. Schoenfelder, A. Mann, *Chem. Commun.* **2001**, *11*, 958–959; d) J. H. Rigby, *Synlett* **2000**, *1*, 1–12; e) A. Dombrowski, M. Nieger, E. Niecke, *Chem. Commun.* **1996**, *14*, 1705–1710; f) J. Tejeda, R. Reau, F. Dahan, G. Bertrand, *J. Am. Chem. Soc.* **1993**, *115*, 7880–7881; g) K. T. Potts, T. Rochanapruk, S. J. Coats, L. Hadjiarapoglou, A. Padwa, *J. Org. Chem.* **1993**, *58*, 5040–5042; h) K. T. Potts, M. O. Dery, *J. Org. Chem.* **1990**, *55*, 2884–2894; i) T. Facklam, O. Wagner, H. Heydt, M. Regitz, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 314–315; j) R. Huisgen, *Z. Chem.* **1968**, *8*, 290–298; k) R. Huisgen, M. Morikawa, K. Herbig, E. Brunn, *Chem. Ber.* **1967**, *100*, 1094–1106.

[8] A. M. Cuadro, J. Valenciano, J. J. Vaquero, J. L. García-Navío, J. Alvarez-Builla, *Tetrahedron* **1993**, *49*, 3185–3192.

[9] Iso(thio)cyanates have proved to be suitable dipolarophiles in several cases: a) R. Palko, Z. Riedl, O. Egyed, L. Fabian, G. Hajos, *J. Org. Chem.* **2006**, *71*, 7805–7812; b) T. Ritter, E. M. Carreira, *Angew. Chem. Int. Ed.* **2005**, *44*, 936–938; c) I. Devi, N. Harsha, P. J. Bhuyan, *Tetrahedron Lett.* **2004**, *45*, 2405–2408.

[10] a) J. Valenciano, A. M. Cuadro, J. J. Vaquero, J. Alvarez-Builla, *Tetrahedron Lett.* **1999**, *40*, 763–766; b) J. Valenciano, A. M. Cuadro, J. J. Vaquero, J. Alvarez-Builla, R. Palmeiro, O. Castaño, *J. Org. Chem.* **1999**, *64*, 9001–9010; c) J. Valenciano, E. Sánchez-Pavón, A. M. Cuadro, J. J. Vaquero, J. Alvarez-Builla, *J. Org. Chem.* **2001**, *66*, 8528–8536.

[11] Y. Tamura, J. Minamikawa, M. Ykeda, *Synthesis* **1977**, 1–17.

[12] "*N*-Aminides" according to Ollis' nomenclature: see ref.[1] . For other nomenclature, see: A. Padwa, ref.[2] or R. Huisgen, R. Temme, *Eur. J. Org. Chem.* **1998**, 387–401.

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