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SYNTHESIS OF NEW MESOMERIC BETAINES CONTAINING A TRIAZOLOPYRIDINIUMOLATE SYSTEM AND THEIR UNEXPECTED FUNCTION AS MASKED ISOCYANATES

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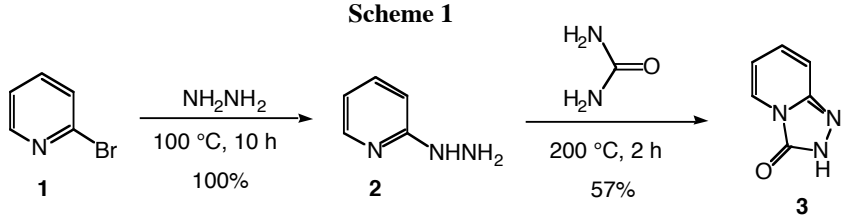
Abstract- A series of mesomeric betaines containing 1-alkylated triazolopyridiniumolate system were synthesized and their cycloaddition with dimethyl acetylenedicarboxylate were examined. An unusual ring-opening reaction occurred to give pyridone derivatives indicating that these betaines act as masked isocyanates.

Mesomeric betaines are widely utilized as useful synthetic intermediates in the construction of a variety of heteropolycycles involving natural products and biologically active compounds. Their utility derives from the fact that most act as 1,3-dipoles and lead to heteropolycycles by one-step reactions with dipolarophiles.[1-3] Hence, the development of novel mesomeric betaines having different arrangements of heteroatoms or different ring skeletons is of great importance from the stand point of synthetic and pharmaceutical chemistry. While, fused pyridine derivatives, for example, [1,2,4]triazolo[4,3-*a*]pyridines,[4] are often found in various biologically active substances and functional materials,[5] only a few examples have been reported in which this unit is embedded into a mesomeric betaine structure.[6] Further applications of mesomeric betaines to reactions with dipolarophiles leading to heterocyclic compounds have not been documented. We have already reported the development of a convenient preparation for mesomeric betaines which contain a pyrrolotriaziniumolate system and their 1,3-dipolar cycloaddition with dipolarophiles leading to ring-enlargement bicyclic products.[7] In this paper, we wish to report facile synthesis of novel mesomeric betaines which contain a triazolopyridiniumolate system and especially their unexpected ring-opening reactions, which clearly show that these betaines function as masked isocyanates in clear contrast with pyrrolotriaziniumolates.

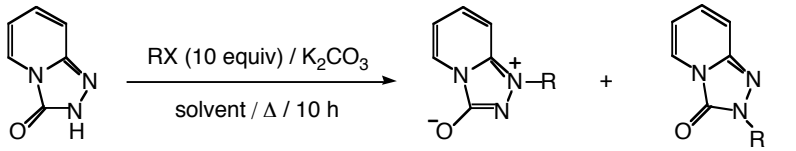
Pyridinotriazol-3-one (**3**, a starting product) was produced from 2-hydrazinopyridine (**2**), which was, in turn, prepared *via* the reaction of 2-bromopyridine (**1**) and hydrazine, with urea at 200 ℃ for 2 h in 57% yield (Scheme 1).[8] IR absorption (1710 cm^{-1}) indicative of a carbonyl group in **3** is consistent with the cyclic urea form.[9] Based on our earlier studies on mesomeric betaines,[7] the quaternization of pyridinotriazolone (**3**) with alkyl halides was carried, giving novel mesomeric betaines. These results are summarized in Table 1. Pyridinotriazolone (**3**) was treated with benzyl bromide (10 equiv) in the presence

Scheme 1



of potassium carbonate (10 equiv) at 80 ℃ for 10 h in dioxane to give 1-benzyl[1,2,4]triazolo[4,3-*a*]pyridinium-3-olate (**4a**) in 60% yield, along with 2-methyl[1,2,4]triazolo[4,3-*a*]pyridin-3-one (**5a**) in 32% yield (entry 1).[10] The structure of compound (**4a**) was qualitatively deduced from spectral data and unambiguously confirmed by X-Ray crystallographic analysis (Figure 1).[11] The N(2)–C(3) and N(1)–C(9) bond lengths (1.33 and 1.32 Å, respectively) indicate double-bond characteristics and the C(3)–N(4) bond length (1.43 Å) is slightly shorter than that of a typical C–N single bond (1.45 Å). These results strongly support the conclusion that **4a** contains a five-membered triazolonium structure. The C=O bond length of 1.24 Å in **4a** was slightly longer than 1.20 Å which is the typical length of a C=O for mesoionic compounds such as *N*-(*p*-bromophenyl)sydonone.[12] A strong absorption at 1666 cm^{-1} in the IR spectrum was observed, which is atypical of a carbonyl group in five-membered cyclic ureas. Collectively, these data are indicative of a larger single-bond character for the C=O bond of **4a**. The ^{1}H-NMR spectrum indicated that four protons on the pyridine ring in **4a** were shifted to lower magnetic field than the corresponding protons in the starting (**3**), reflecting the mesomeric effect of the cation in **4a**. All the other spectral data were fully consistent with the mesomeric betaine structure of **4a**.

Table 1. Quaternization of Pyridinotriazolone (3) with Alkyl halides



entry	RX	solvent	temp. (℃)	yield (%)[a]				
				4		5		3
1	$PhCH_2Br$	dioxane	80	**4a**	60	**5a**	32	0
2	MeI	dioxane	40	**4b**	10	**5b**	20	65
3	MeI	CH_2Cl_2	40	**4b**	19	**5b**	9	45
4	MeI	acetone	40	**4b**	0	**5b**	100	0

[a] Isolated yields

The quaternization reaction of **3** with methyl iodide (10 equiv) also afforded a 1-methylated analog (**4b**), along with a 2-methylated pyridin-3-one (**5b**) in 10% and 20% yields, respectively (entry 2). In the case where CH_2Cl_2 was used as a solvent, the yield of **4b** was slightly increased to 19% and that of **5b** reduced mto 9% (entry 3). It is noteworthy that, when a polar solvent such as acetone was employed, only the 2-alkylated product (**5b**) was obtained in quantitative yield (entry 4). The mesomeric structure of compound

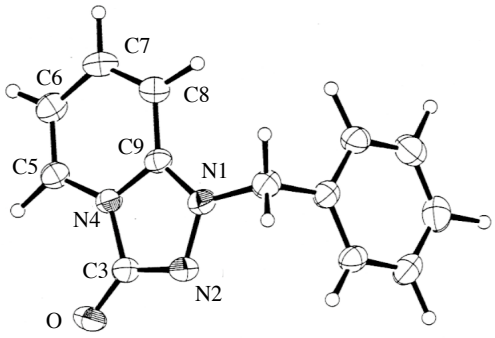
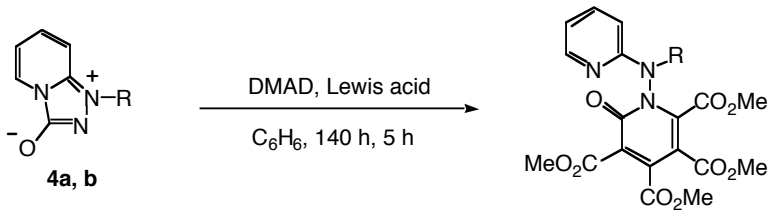


Figure 1. ORTEP view of betaine (**4a**)

(**4b**) was also defined by spectral data and elemental analysis. In contrast, spectral data for (**5a**,**b**) are in good agreement with the nonaromatic structure which is formed as a result of the alkylation of the nitrogen on the 2-position.

It is quite important to clarify whether mesomeric betaines (**4a**,**b**) act as 1,3-dipoles or not. Thus, the cycloaddition reaction of betaines (**4**) with a typical dipolarophile as dimethyl acetylenedicarboxylate (DMAD) was investigated. These results are listed in Table 2. When a solution of **4a** and DMAD (2 equiv) in benzene was heated at 140 ℃ for 5 h, no cycloaddition products were observed (entry 1). In an attempt

Table 2. The reactions of betaines (4) with DMAD in the presence of Lewis acids leading to Pyridone derivatives (6) [a]



entry	R	DMAD (eq)	Lewis acid (0.1 eq)	yield (%)[b]
1	**4a** $PhCH_2$	2	—	0
2	**4a** $PhCH_2$	2	$MgBr_2 \cdot 6H_2O$	5
3	**4a** $PhCH_2$	4	$MgBr_2 \cdot 6H_2O$	27
4	**4a** $PhCH_2$	10	$MgBr_2 \cdot 6H_2O$	42
5	**4a** $PhCH_2$	10	$MgBr_2 \cdot 6H_2O$ (1.0 eq)	15
6	**4a** $PhCH_2$	10	$AlCl_3$	31
7	**4a** $PhCH_2$	10	$ZnBr_2$	38
8	**4b** Me	10	$MgBr_2 \cdot 6H_2O$	51

[a] In sealed tubes. [b] Isolated yield.

to accelerate the cycloaddition reaction, the addition of a Lewis acid (0.1 equiv) such as $MgBr_2 \cdot 6H_2O$ was then examined. Interestingly, an unexpected reaction occurred to afford a ring-opening adduct, 1-(*N*-2-pyridylbenzylamino)-3,4,5,6-tetra(methoxycarbonyl)pyrid-2-one (**6a**) in 5% yield (entry 2).[10] The structure of **6a** was confirmed by X-Ray crystallographic analysis as shown in Figure 2.[13] When the amount of DMAD was increased to 10 equiv, the yield of **6a** was improved to 42% (entry 4). Other Lewis

acids, such as $AlCl_3$ and $ZnBr_2$ were also effective in improving the yield of **6a** (entries 6, 7). Of the reaction conditions examined to date, the reaction of **4b** with DMAD provided the pyridone derivative (**6b**) in the best yield (51%, entry 8).

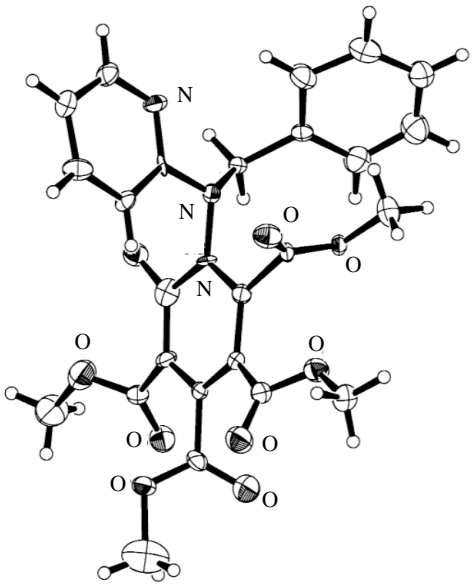
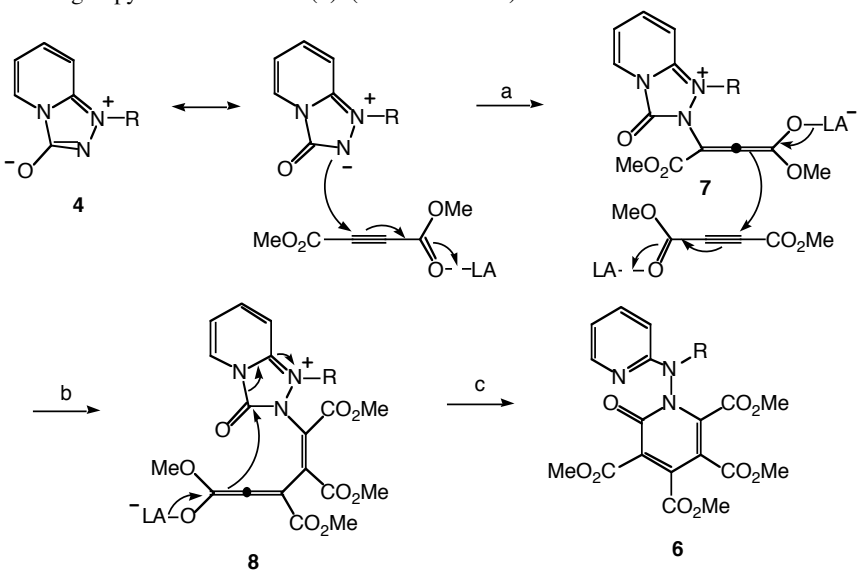


Figure 2. ORTEP view of pyridone detivative (**6a**)

A plausible mechanism for the formation of the pyridone derivatives (**6**) is shown in Scheme 2. A nucleophilic attack of the amido anion in **4** on DMAD, which is activated by a Lewis acid, would give rise to an allenic intermediate (**7**) (path a). The thus formed intermediate (**7**) adds to another activated DMAD to form a triazolopyridinone intermediate (**8**) (path b), followed by the intramolecular nucleophilic attack of the terminal carbanion in **8** to the carbonyl carbon in the triazolone ring to give the pyridone (**6**) (path c). The pyridone ring in the final product (**6**) would be formed by the 1 : 2 cycloaddition reaction of an isocyanate with DMAD. Hence, these betaines act as masked isocyanates in the proposed mechanism.

Scheme 2. Plausible reaction mechanism of the reaction of betaine (**4**) with DMAD leading to pyridone derivative (**6**). (LA: Lewis acid)



Thus far, we have succeeded in the synthesis of novel mesomeric betaines, which consist of a triazolopyridiniumolate system and found that the reaction of these types of betaines with DMAD unexpectedly affords pyridone derivatives. This suggests that the betaines have a low degree of 1,3-dipolar character and, function as masked isocyanates in these reactions. Further reactions with various dipolarophiles and the development of related mesomeric betaines are under investigation.

ACKNOWLEDGMENT

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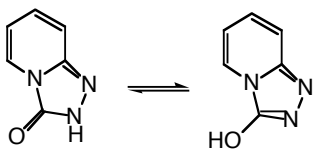
9. The compound (**3**) was detected in its enol form in a polar solvent such as DMSO (*vide infra*). Spectral data for **3**: mp 201 ℃ (colorless crystals from hex-CH_2Cl_2); IR (KBr, cm^{-1}) 3400 (NH), 3203 (NH), 1710 (C=O); ^{1}H-NMR (270 MHz, DMSO-d_6) δ 6.52-6.58 (m, 1H, H-7), 7.15-7.18 (m, 2H,



H-6 and H-8), 7.77-7.8 (m, 1H, H-5), 12.43 (br s, 1H, OH); ^{13}C-NMR (68 MHz, DMSO-d_6) δ 110.4, 115.5, 123.7, 130.0, 142.5, 159.6; MS (EI) *m/z* 135 (M^+); HR-MS. Calcd for $C_6H_5N_3O$: 135.0433 Found: 135.0428.

10. All new compounds are fully characterized. Data for selected compounds; **4a**: mp 166-168 °C (colorless crystals from hex-CH_2Cl_2); IR (KBr, cm^{-1}) 1666; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.30 (s, 2H, CH_2), 6.86 (t, 1H, *J* = 6.9 Hz, H-6), 7.19 (d, 1H, *J* = 9.2 Hz, H-8), 7.34-7.37 (m, 5H, Ph), 7.46 (dd, 1H, *J* = 9.2 Hz, *J* = 6.9 Hz, H-7), 8.22 (d, 1H, *J* = 6.9 Hz, H-5); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 52.6, 108.5, 112.5, 125.6, 127.7, 128.6, 129.0, 133.9, 134.1, 138.5, 154.1; MS (EI) *m/z* 225 (M^+) 91 ($PhCH_2^+$); Anal. Calcd for $C_{13}H_{11}N_3O\cdot0.5H_2O$: C, 66.65; H, 5.16; N, 17.94. Found: C, 66.51; H,5.19; N, 17.88. **5a**: mp 145-147 °C (colorless crystals from hex-CH_2Cl_2); IR (KBr, cm^{-1}) 1702 (C=O); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.17 (s, 2H, CH_2), 6.45 (t, 1H, *J* = 6.9 Hz, H-6), 7.06 (d, 1H, *J* = 6.9 Hz, H-8), 7.09 (t, 1H, *J* = 6.9 Hz, H-7), 7.26-7.42 (m, 5H, aromatic), 7.77 (d, 1H, *J* = 6.9 Hz, H-5); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 49.7, 110.5, 115.4, 123.7, 128.0, 128.3, 128.7, 129.8, 135.8, 141.6, 148.9; MS (EI) *m/z* 225 (M^+), 91($PhCH_2^+$); Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.18; H, 4.97; N, 18.77. **6a**: mp 127-129 °C (colorless crystals from hex-PhH); IR (KBr, cm^{-1}) 1722, 1684; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.49 (s, 3H, Me), 3.78 (s, 3H, Me), 3.87 (s, 3H, Me), 3.93 (s, 3H, Me), 4,51 (d, 1H, *J* = 16 Hz, PhC$\underline{H}_2$), 5.72 (d, 1H, *J* = 16 Hz, PhC$\underline{H}_2$), 6.57 (d, 1H, *J* = 8.3 Hz), 6.93 (dd, 1H, *J* = 8.3 Hz, *J* = 5 Hz), 7.26-7.36 (m, 5H, Ph), 7.55 (dd, 1H, *J* = 8.3 Hz, *J* = 5 Hz), 8.29 (d, 1H, *J* = 5 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 53.2, 53.3, 56.7, 104.6, 109.0, 118.0, 123.4, 127.6, 128.2, 128.4, 136.2, 137.9, 145.8, 147.8, 151.3, 156.4, 157.4, 159.9, 161.9, 163.4, 165.0; MS (CI) *m/z* 510 (M^++1); Anal. Calcd for $C_{25}H_{23}N_3O_9$: C, 58.94; H, 4.55; N, 8.25. Found: C, 59.10; H, 4.46; N, 8.22.
11. X-Ray crystallographic data[14] for **4a**: $C_{13}H_{11}N_3O$, *M* = 225.09, colorless prismatic, orthorhombic, space group Pccn (alt. setting No. 56), *a* = 12.356 (3) Å, *b* = 14.074 (3) Å, *c* = 13.102 (3) Å, α = 90.00°, β = 90.00°, γ = 90.00°, *V* = 2278 (1) Å^3, *Z* = 4, *Dc* 0.71 g/cm^{-1}, *F*(000) = 360.00, μ(Cu Kα) = 5.03 cm^{-1}, graphite monochromated CuKα (λ = 1.54178 Å), *T* = 14 °C. Final discrepancy factor: R = 0.052 and Rw = 0.058.
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12. X-Ray crystallographic data[14] for **6a**: $C_{25}H_{23}N_3O$, M = 509.47, colorless plates, triclinic, space group P1 (alt. setting No. 2), *a* = 10.362 (8) Å, *b* = 15.226 (9) Å, *c* = 8.615 (8) Å, α = 90.33 (6)°, β = 109.04 (6)°, γ = 75.49 (5)°, *V* = 1239 (1) Å^3, *Z* = 2, *Dc* 1.365 g/cm^{-1}, *F*(000) = 820.00, μ(Mo Kα) = 0.77 cm^{-1}, graphite monochromated MoKα (λ = 0.71069 Å), *T* = 23 °C. Final discrepancy factor: R = 0.110 and Rw = 0.116.
14. The structures of **4a** and **6a** were solved by the direct method (SHELEX-86).