

Amidine-Enediamine Tautomerism. A Novel Michael-type Reaction

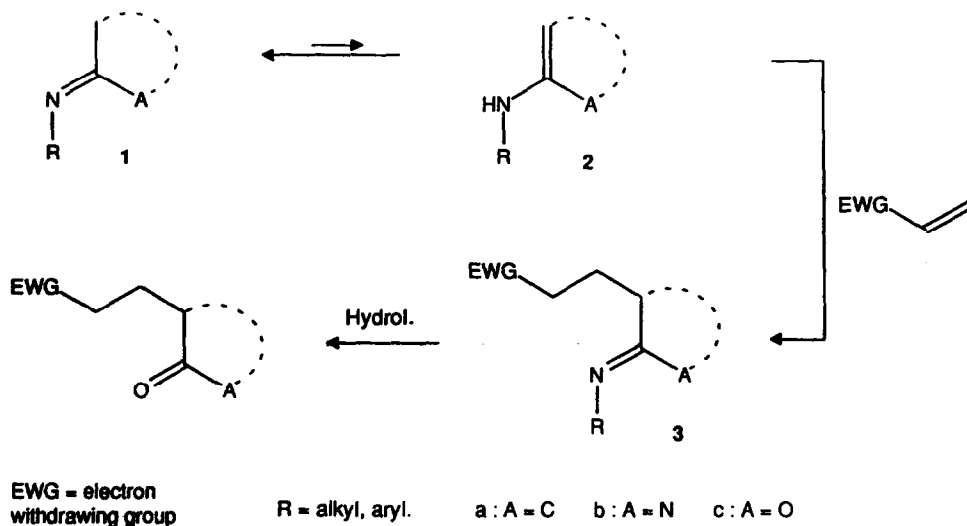
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Michael-type reaction ; α -alkylated cyclic amidines ; methyl acrylate.

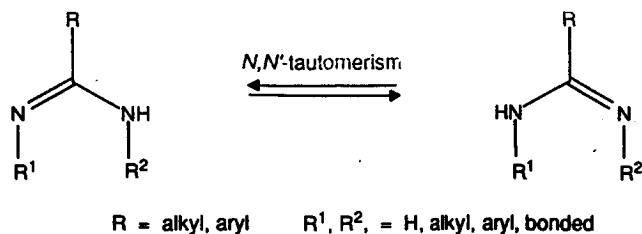
Abstract: Cyclic amidines **4** and **11** have been shown to be in *N,C*-tautomeric equilibrium with the corresponding ene-1,1-diamines which can be C-alkylated by methyl acrylate, leading respectively to the corresponding functionalized substituted amidines **6** (or **7**) and **12**.

The useful Michael-type addition of imines **1a**, reacting as their secondary enamine tautomers **2a**, is well documented¹. It was of interest to explore the possibility that a similar behavior could be observed with amidines **1b** and lactams **1c**.



In this Letter we report our results concerning cyclic amidines **1b**, showing that the reaction mentioned does indeed occur, and leads to the alkylated cyclic amidines **3b**.

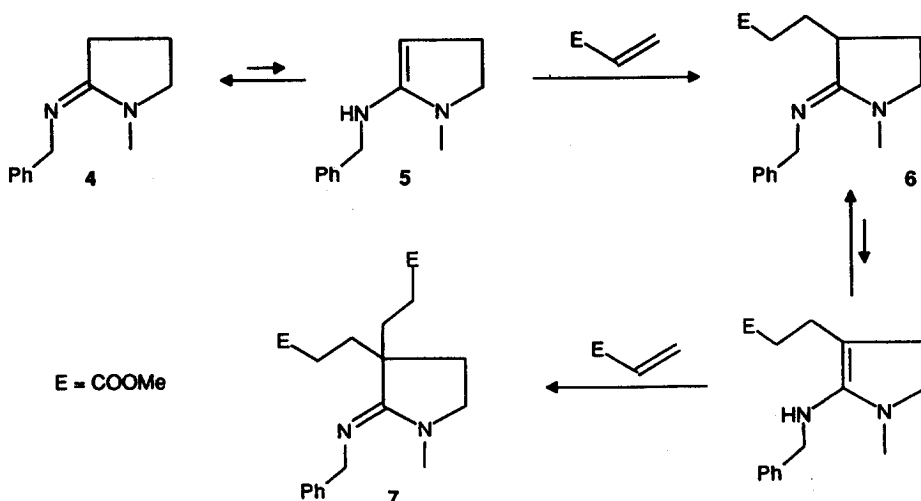
A bibliographic survey shows that although the amidine *N,N'*-tautomerism has been the object of numerous studies², no *N,C*-tautomerism such as **1b** \rightleftharpoons **2b**, has been reported.



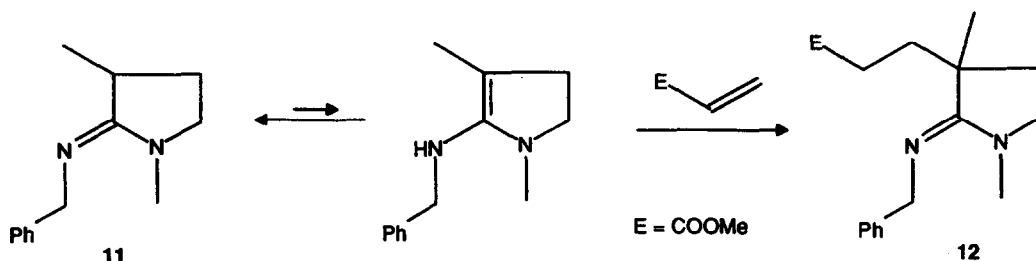
The proof of the existence of a *N,C*-tautomeric equilibrium with *N,N'*-trisubstituted amidines is now substantiated. Thus, equilibrium $4 \rightleftharpoons 5$ has been demonstrated, at least in methanolic medium, by the same method as used before to prove the existence of imine-secondary enamine tautomerism^{1a,b}, i.e. by ¹H NMR spectroscopy of a CD₃OD solution of cyclic amidine **4**³. After one hour at room temperature, there is a complete disappearance of the triplet (2.35 ppm) corresponding to the two hydrogen atoms in the α -position relative to C = N (the half-disappearance occurs in ca. 5 minutes). This fact indicates that the *N,C*-tautomerism is efficient, although at equilibrium (as for secondary enamines^{1a,b}) the ene-1,1-diamine form **5** should be present at less than 3% since no vinyl proton is detected in the ¹H NMR spectrum of amidine **4** in CCl₄.

N,N'-unsubstituted or monosubstituted amidines, as shown on the scheme above (R = alkyl ; R¹ = H, aryl ; R² = H) react with electrophilic olefins by nucleophilic *N*-attack⁵. To our knowledge, syntheses of compounds which could have arisen from a nucleophilic *C*-attack of an amidine on an electrophile have not been reported.

Preliminary experiments with amidine **4**³ and methyl acrylate having shown that both mono- and bis-adducts are formed, reaction conditions were established to obtain either **6** or **7**. Thus, an essentially quantitative yield of mono-adduct **6** is observed when methyl acrylate (containing a catalytic amount of hydroquinone) is heated in a sealed tube at 150 °C for 16h with four equivalents of amidine **4** (excess recoverable)⁶. On the other hand, when amidine **4** is heated in the same conditions with four equivalents of methyl acrylate, the bis-adduct **7** is obtained in 82% yield⁸.



When compound **11**³ (a starting amidine already substituted in the α -position) is reacted in the same conditions with one equivalent of methyl acrylate, adduct **12** is obtained quantitatively¹¹.



A striking difference of reactivity towards methyl acrylate is observed with amidines **4** or **11** and imines **1a** since the latter typically require three days at room temperature to be completely converted¹, in which conditions amidines **4** and **11** do not react. Either an ene-1,1-diamine such as **5** is less nucleophilic than secondary enamines, or it is present at a very low concentration at equilibrium.

Thus, a previously unreported tautomeric process has been uncovered with amidines, which allows to achieve C-Michael additions leading to potentially useful functionalized nitrogen-containing compounds. We are presently exploring the scope and other aspects of this novel reaction.

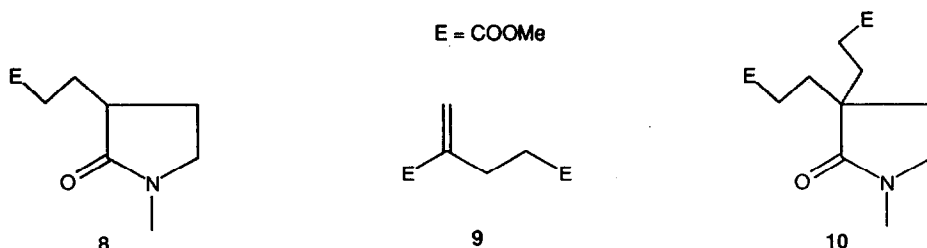
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- Compounds **4** and **11** are obtained in 66% and 60% yield respectively from 1-methylpyrrolidone and 1,3-dimethylpyrrolidone according to the general method⁴ using POCl₃ and then a primary amine (here benzylamine). **4**: bp 115 °C / 0.02 Torr. MS: 188 (M⁺). IR (neat): 1645 cm⁻¹. ¹H NMR 90 MHz (CCl₄): 1.60-2.00, m, 2H; 2.25, t, 2H; 2.80, s, 3H; 3.15, t (J = 6.5 Hz), 2H; 4.25, s, 2H; 6.90 - 7.35, m, 5H. **11**: bp 120 °C / 0.02 Torr. MS: 202 (M⁺). IR (neat): 1650 cm⁻¹. ¹H NMR 300 MHz (CDCl₃): 1.10, d, 3H; 1.10-1.20, m, 1H; 1.55-1.65, m, 1H; 2.05-2.20, m, 1H; 2.90, s, 3H; 2.90-3.05, m, 1H; 3.15-3.25, m, 1H; 3.35-3.45, m, 1H; 4.48, d (J = 15.5 Hz), 1H; 4.57, d (J = 15.5 Hz), 1H; 7.15-7.45, m, 5H.
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5 Weis, A.L.; Zamir, D. *J. Org. Chem.* 1987, 52, 3421-3425. Kashima, C.; Shimizu, M.; Omote, Y. *J. Heterocycl. Chem.* 1989, 26, 251-254.

6 Experiments were achieved at the multi-gram scale. TLC and GC respectively show a total absence of polymeric products and the complete disappearance of methyl acrylate. Distillation affords excess amidine 4 followed by mono-adduct 6 : bp - 140 °C / 0.02 Torr. MS : 274 (M^+). IR (neat) : 1735, 1645 cm^{-1} . ^1H NMR 250 MHz (CDCl_3) : 1.55-1.75, m, 2H ; 1.85-2.15, m, 2H ; 2.30-2.50, m, 2H ; 2.90, s + m, 3H + 1H ; 3.15-3.25, m, 1H ; 3.30-3.40, m, 1H ; 3.67, s, 3H ; 4.49, d ($J = 15.0$ Hz), 1H ; 4.60, d ($J = 15.0$ Hz), 1H ; 7.15 - 7.40, m, 5H. ^{13}C NMR 20 MHz (CDCl_3) : 25.44, 25.99, 31.27, 31.62, 37.08, 49.02, 51.52, 53.78, 125.92, 127.01, 128.03, 142.98, 165.03, 173.21. Cyclic cleavage and ester saponification of amidine 6 were achieved in strong basic conditions. The resulting amino-acid-amide was in turn hydrolyzed in strong acidic medium to give the corresponding amino-diacid. The latter was then esterified in acidic methanol to lead, after spontaneous cyclization through basic work-up, to lactam 8⁷ : bp - 105 °C / 0.02 Torr. IR (neat) : 1735, 1680 cm^{-1} . ^1H NMR 90 MHz (CCl_4) : 1.50 - 2.55, m, 7H ; 2.75, s, 3H ; 3.25, m, 2H ; 3.60, s, 3H.

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8 TLC reveals the total absence of polymeric products while GC shows the complete disappearance of starting amidine 4 and the presence of a small amount of mono-adduct 6 accompanying the bis-adduct 7. Distillation affords the known methyl acrylate dimer 9⁷ : bp 101 °C / 15 Torr. MS : 172 (M^+). IR (neat) : 1740, 1715, 1630 cm^{-1} . ^1H NMR 90 MHz (CCl_4) : 2.40 - 2.60, m, 4H ; 3.65, s, 3H ; 3.75, s, 3H ; 5.60, d ($J = 1.5$ Hz), 1H ; 6.15, br s, 1H ; litt.⁹ : bp 74 -77 °C / 9.5 Torr. ^1H NMR (CDCl_3) : 2.62, m, 4H ; 3.70, s, 3H ; 3.80, s, 3H ; 5.64, s, 1H ; 6.24, s, 1H. Then distillation yields a small amount of a light fraction followed by bis-adduct 7 : bp - 160 °C / 0.02 Torr. MS : 360 (M^+). IR (neat) : 1740, 1640 cm^{-1} . ^1H NMR 250 MHz (CDCl_3) : 1.75-1.95, m, 4H ; 2.15-2.50, m, 6H ; 2.85, s, 3H ; 3.20, t ($J = 7.0$ Hz), 2H ; 3.63, s, 6H ; 4.68, s, 2H ; 7.15-7.45, m, 5H. ^{13}C NMR 20 MHz (CDCl_3) : 29.78, 31.62, 32.15, 33.08, 48.25, 48.61, 49.94, 51.60, 125.94, 126.98, 128.04, 142.85, 161.25, 173.39. Amidine 7 was converted to the known lactam 10⁷ : IR (neat) : 1735, 1685 cm^{-1} . ^1H NMR 90 MHz (CCl_4) : 1.60-2.00, m, 6H ; 2.20, m, 4H ; 2.75, s, 3H ; 3.25, t ($J = 7.0$ Hz), 2H ; 3.60, s, 6H ; litt.¹⁰ : IR (neat) : 1730, 1685 cm^{-1} . ^1H NMR (CDCl_3) : 2.75, s, 3H ; 3.27, t ($J = 7.0$ Hz), 2H ; 3.65, s, 6H.

9 Dimer 9 has been prepared by refluxing a solution of methyl acrylate in *t*-butanol in presence of hydroquinone and tributylphosphine : Kagan, J.; Tolentino, L. *J. Org. Chem.* 1975, 40, 3085-3093.

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11 Adduct 12 : bp 120 °C / 0.02 Torr. MS : 288 (M^+). IR(neat) : 1740, 1645 cm^{-1} . ^1H NMR 300 MHz (CDCl_3) : 1.28, s, 3H ; 1.65 - 1.75, m, 1H ; 1.90 - 2.00, m, 2H ; 2.15 - 2.45, m, 3H ; 2.85, s, 3H ; 3.18, t ($J = 6.5$ Hz), 2H ; 3.62, s, 3H ; 4.63, d ($J = 16.0$ Hz), 1H ; 4.75, d ($J = 16.0$ Hz) 1H ; 7.15 - 7.37, m, 5H. ^{13}C NMR 75.5 MHz (CDCl_3) : 24.73, 30.57, 33.49, 34.06, 35.73, 45.50, 48.96, 50.80, 52.34, 126.63, 127.63, 128.73, 143.62, 164.87, 174.41.

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