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An efficient synthesis of 2-amino-3-cyano-2-pyrrolin-4-ones, via the corresponding open chain tautomers (aminoacetylmalononitriles)

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Abstract—Malononitrile has been found to be acylated effectively using *N*-protected glycines by simultaneous activation of an amino acid carbonyl group and a malononitrile methylene group using carbonyl diimidazole (CDI). The corresponding aminoacetonitriles were isolated as enols and/or as their tautomeric forms, 2-amino-3-cyano-2-pyrrolin-4-ones.

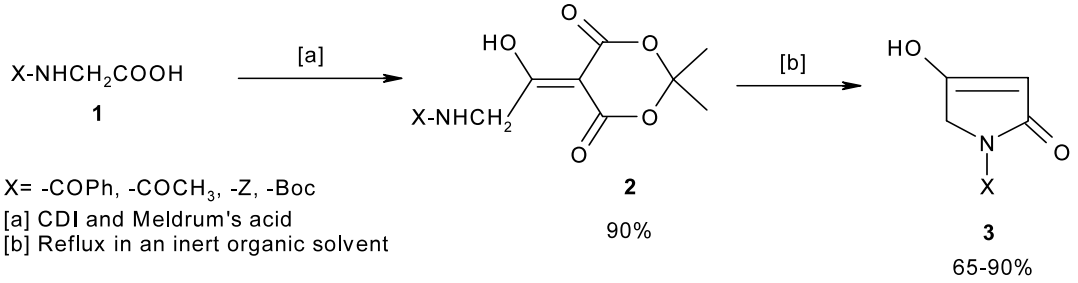
Recently 2-pyrrolin-4-ones have been found in a wide range of biologically active compounds,[1] including HIV protease inhibitors with antiviral activity, as well as in useful antispasmodic and antihypertensive drugs. For this reason, 2-amino-3-cyano-2-pyrrolin-4-ones must be considered to be of interest as potential prodrugs.

In a previous communication,[2] we reported the *C*-acylation of Meldrum's acid with *N*-protected glycines (via their imidazolides), using 1,1′-carbonyl diimidazole (CDI). The corresponding *C*-acylation products **2** were isolated in high yields (ca. 90%) and were readily converted to *N*-protected tetramic acids **3** (Scheme 1).

We now report an investigation into the *C*-acylation reactions of an exceptionally acidic methylene compound, malononitrile, also using *N*-protected glycines as the acylating reagents. Malononitrile has been used[3] in acylation reactions with different acylating agents such as azlactones and acyl halides, usually in the presence of a base.

We here describe a particularly simple and convenient acylation reaction of malononitrile using imidazolides of *N*-protected glycines **1**[4] (Scheme 2). The imidazole liberated during formation of the amino acid imidazolide is sufficiently basic for formation of the malononitrile anion. It was found that either the *N*-protected aminoacetylmalononitriles **4a** and **4b**[5] or the 1-Boc-2-amino-3-cyano-2-pyrrolin-4-one **5d**[6] were isolated.

The fact that the cyclic tautomer **5d** was isolated instead of the corresponding acylation product **4d**



Scheme 1.

Keywords: 2-amino-3-cyano-2-pyrrolin-4-ones; aminoacetylmalononitriles; tautomers; CDI.
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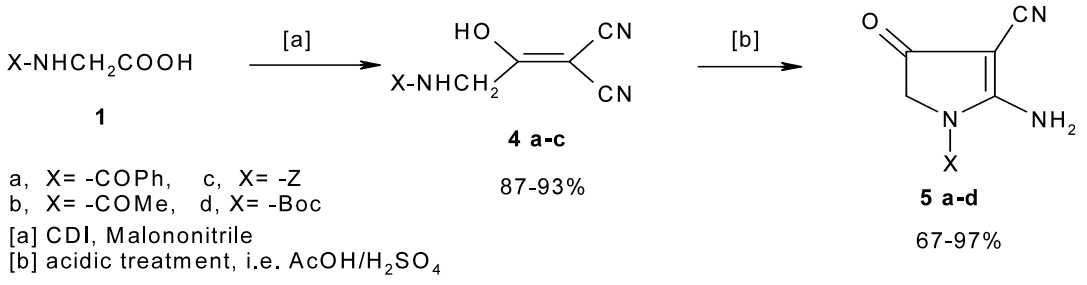
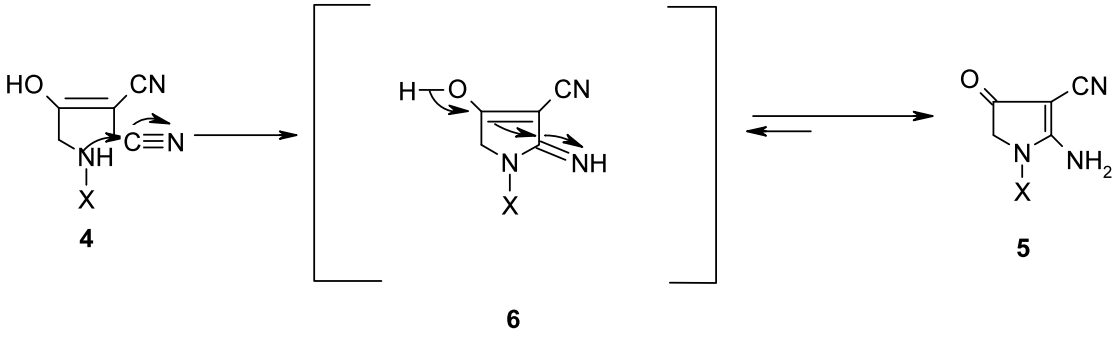


Scheme 2.



Scheme 3.

established a relationship between the substituent on the amino acid nitrogen and the structure of the isolated tautomer, i.e. **4** or **5**.

The acylation of *N*-Z-glycine gave a mixture of **4c**:**5c** isolated in the molar ratio 5:1, as estimated by ^{1}H NMR. The presence of signals assigned to **5c**[6] and singlets at δ 4.13 ppm for the methylene and at δ 5.13 for the benzylic methylene of **4c** permitted their characterization. This mixture was converted quantitatively according to the general procedure,[7] into the product **5c**.

The isolation of the different tautomeric forms **4** and **5** is explained by the differing nitrogen basicities (Scheme 3). For the group X = -Boc in which the carbamate nitrogen is more nucleophilic, the cyclic tautomer **5d** is favored (obviously via the intermediate enol-imine **6**). On the contrary, for the groups X = -COPh and -COMe, where the amide nitrogen is a weak nucleophile, the open chain tautomers **4** are preferred. When X = Z ($PhCH_2OCO$-), the behavior appears to be closer to the -COPh and -COMe groups, even though a carbamate nitrogen is present.

The conversion of the acylmalononitriles **4a**–**c** into the corresponding pyrrolinones **5a**–**c**, was effected by simple acid treatment.[7] This was explained by protonation of the polar -CN group, which consequently becomes more susceptible to nucleophilic attack. This cyclization is a 5-*exo*-dig cyclization which is favored stereochemically according to Baldwin rules.[8]

It must be pointed out, that the acylation products **4a** and **4b** exist exclusively in their enol forms **4** as revealed from IR and NMR spectra. The absence of a ketonic carbonyl absorption in their IR spectra, as well as the absence of a methine proton and the simultaneous presence of a very broad -OH signal at low field in their NMR spectra are further proof of the enolic forms of **4**. In agreement with these observations, compounds **4** give an intense red color with an aqueous solution of ferric chloride.

In conclusion, the *C*-acylation of malononitrile with *N*-protected glycines has been performed by a simple experimental procedure using the imidazolide activation method. The acylation compounds were converted into 2-amino-3-cyano-2-pyrrolin-4-ones. The application of the imidazolide activation to acylation reactions with chiral *N*-protected amino acids is currently being investigated.

References

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4. Typical procedure for the *C*-acylation of malononitrile: To a suspension of the *N*-protected glycine **1** (10 mmol) in 40 ml dichloromethane, 1,1′-carbonyldiimidazole (10.1 mmol) was added. The reaction flask was protected with a calcium chloride drying tube and the mixture was stirred for typically 1 h, until the gas (CO_2) evolution ceased. Malononitrile (10 mmol) was then added to the solution and the mixture was stirred at room temperature for an additional 1 h. The solution (or suspension), was then concentrated under vacuum and the semi-solid residue was diluted with water. The solution was cooled with ice-water and acidified dropwise with 10% hydrochloric acid with vigorous stirring for ca. 15 min. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried (magnesium sulfate) and concentrated to a solid residue.
5. Isolation of open chain tautomers **4a** and **4b** (*N*-protected-aminoacetylmalononitriles). The general *C*-acylation procedure[4] was followed and compounds **4a** and **4b** were obtained as solids residues, which proved to be almost pure (^{1}H NMR). Compound **4a**: The solid residue (93% yield), mp 138–142°C, was recrystallized from acetic acid to yield a crystalline solid mp 144–148°C. Anal. calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.40; H, 3.99; N, 18.48. IR (Nujol mull, cm^{-1}): 3400, 2230, 1640 and 1530; ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.38 (d, $J=6$ Hz, 2H, -CH_2-), 7.20–8.00 (m, 5H, Ph-), 8.66 (m, 1H, -NH-), 9.80 (br s, 1H, enolic -OH). Compound **4b**: The solid residue (87% yield), mp >220°C, was recrystallized from ethyl acetate to yield a crystalline solid mp>220°C. Anal. calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 51.15; H, 4.18; N, 25.72. IR (Nujol mull, cm^{-1}): 3357, 2232, 1624 and 1557; ^{1}H NMR (60 MHz, $CDCl_3$/DMSO-d_6): δ 2.05 (s, 3H, -CH_3), 4.16 (d, $J=5$ Hz, 2H, -CH_2-), 8.30 (br m, 1H, -NH-), 9.40 (s, 1H, enolic -OH).
6. Isolation of cyclic tautomer **5d** (1-Boc-2-amino-3-cyano-2-pyrrolin-4-one). The typical *C*-acylation procedure[4] was followed and compound **5d** was obtained as a solid residue which proved to be almost pure (^{1}H NMR). Compound **5b**: The isolated solid (75% yield), mp >210°C, was recrystallized from acetic acid to yield a crystalline solid mp >210°C. Anal. calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.72; H, 3.99; N, 25.17. IR (Nujol mull, cm^{-1}): 3300, 3190, 2210, 1710 and 1670; ^{1}H NMR (60 MHz, DMSO-d_6): δ 2.23 (s, 3H, -CH_3), 4.27 (s, 2H, ring -CH_2-), 9.13 and 9.38 (two br s, 2H, -NH_2). Compound **5c**: The solid residue (97% yield), mp 183–187°C, was recrystallized from acetic acid to yield a crystalline solid mp 189–192°C. Anal. calcd for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31; N, 16.33. Found: C, 60.96; H, 4.20; N, 16.24. IR (Nujol mull, cm^{-1}): 3380, 2215, 1728, 1680 and 1615; ^{1}H NMR (60 MHz, $CDCl_3$/DMSO-d_6): δ 4.09 (s, 2H, ring -CH_2-), 5.27 (s, 2H, benzylic -CH_2-), 7.40 (s, 5H, Ph-), 8.55 and 9.45 (two br s, 2H, -NH_2). Compound **5d**: The solid residue (96% yield), mp 163–167°C dec., was recrystallized from acetic acid to yield a crystalline solid mp 170°C dec. Anal. calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.69; H, 5.73; N, 18.87. IR (Nujol mull, cm^{-1}): 3200, 2210, 1725, and 1620; ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.57 (s, 9H, -Boc), 4.04 (s, 2H, ring -CH_2-), 7.72 and 8.54 (two br s, 2H, -NH_2).
7. General procedure for the transformation (tautomerization) **4a**→**5a**, **4b**→**5b** and **4c**+**5c**→**5c**. To a solution of the acylaminoacetylmalononitrile **4a**, **4b** or **4c**+**5c** (5 mmol) in acetic acid (8 ml), four drops of concentrated sulfuric acid were added and the solution was heated in a steam bath for 1.5 h. After cooling, the precipitate was filtered and washed with ethanol to give compound **5a**, **5b** or **5c**, which proved to be almost pure (^{1}H NMR). Compound **5a**: The isolated solid (67% yield), mp 189–192°C, was recrystallized from ethanol to yield a crystalline solid mp 196°C. Anal. calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.14; H, 3.70; N, 18.34. IR (Nujol mull, cm^{-1}): 3345, 3111, 2214, 1685, and 1622; ^{1}H NMR (60 MHz, DMSO-d_6): δ 4.12 (s, 2H, ring -CH_2-), 7.70 (s, 5H, Ph-), 9.33 and 9.66 (two br s, 2H, -NH_2).
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