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The Synthetic Utility of Amide and Amidine Derivatives Containing Polycarbonyl Moieties in the Synthesis of β-Aminoenones[a]

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Summary. The application of derivatives of the easily decomposing weak bases formamide, semicarbazide, urea, or formamidine in the synthesis of β-aminoenones is described. These compounds readily undergo transamination with strong bases, thus opening the way to various heterocyclic compounds.

Keywords. Polycarbonyls; Amides; Amidines; β-Aminoenones; Transamination.

Introduction

The decomposition of formamide into ammonia and carbon oxide in the condensation–reduction reaction with carbonyl compounds has been widely used to prepare amine derivatives [1–4]. In addition to the synthesis of enaminones [5–8] and pyrimidines [9–11], many heterocyclic derivatives have been prepared by this method. As part of our ongoing efforts to obtain the pyrrolo[3,4-*d*]pyrimidine system, a general and efficient synthesis of 1-phenyl-4-(phenylaminomethylidene)-pyrrolidine-2,3,5-trione *via* condensation or transamination is reported. As starting materials, 4-(phenylhydroxymethylidene)-pyrrolidine-2,3,5-trione or enaminone derivatives and easily decomposing formamide, amidine, urea, or semicarbazide derivatives were used. It has been reported that the basicity of nitrogen bases limits the condensation reaction of the latter with a polycarbonyl compound. Thus, very weak bases like urea and thiourea did not form any product in ethanolic solution, but strongly basic compounds like guanidine, triphenylguanidine, and 1,5- or 1,6- aliphatic diamines gave thermally stable salts up to 260°C, regardless of the reaction conditions [12–15].

Results and Discussion

Upon reaction with formamide which was also used as solvent, polycarbonyl derivatives **1** gave exclusively the enaminones **2** (Scheme 1). The same result was

[a] Dedicated to Prof. Dr. W. Żankowska-Jasińska on the occasion of her 80th birthday

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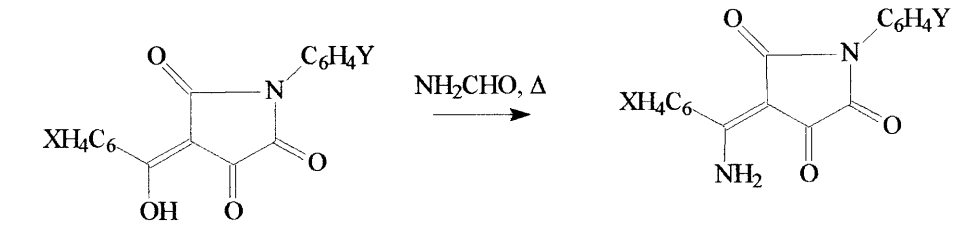
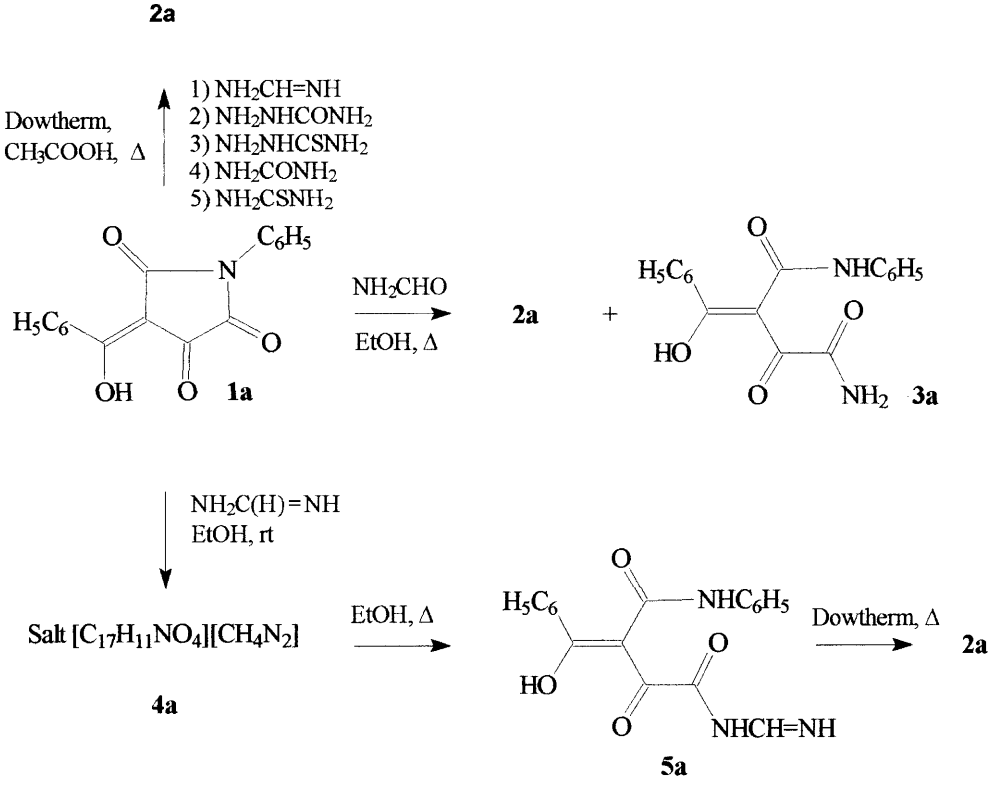


1a: *X*, *Y* = H
1b: *X* = 4-Cl, *Y* = H
1c: *X* = H, *Y* = 4-CH_3

2a: *X*, *Y* = H
2b: *X* = 4-Cl, *Y* = H
2c: *X* = H, *Y* = 4-CH_3

Scheme 1



Scheme 2

obtained when the reaction of **1a** was performed with a variety of weak bases such as urea, formamidine, or semicarbazide derivatives in boiling dowtherm with addition of acetic acid to facilitate the removal of the hydroxyl group (Scheme 2).

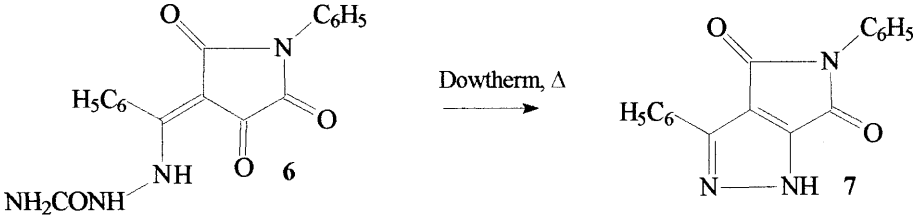
Replacement of the high-boiling solvent by ethanol caused the formation of an additional open-chain derivative. Thus, reaction of **1a** with formamide in boiling ethanol resulted in the formation of **2a** and **3a**, the latter being the product of the succinimide N1–C2 bond cleavage. Furthermore, at room temperature, **1a** with

formamidine yielded the salt **4a** which converted quantitatively to the intermediate **5a** under these conditions. The latter underwent further reaction in boiling dowtherm to **2a** (Scheme 2).

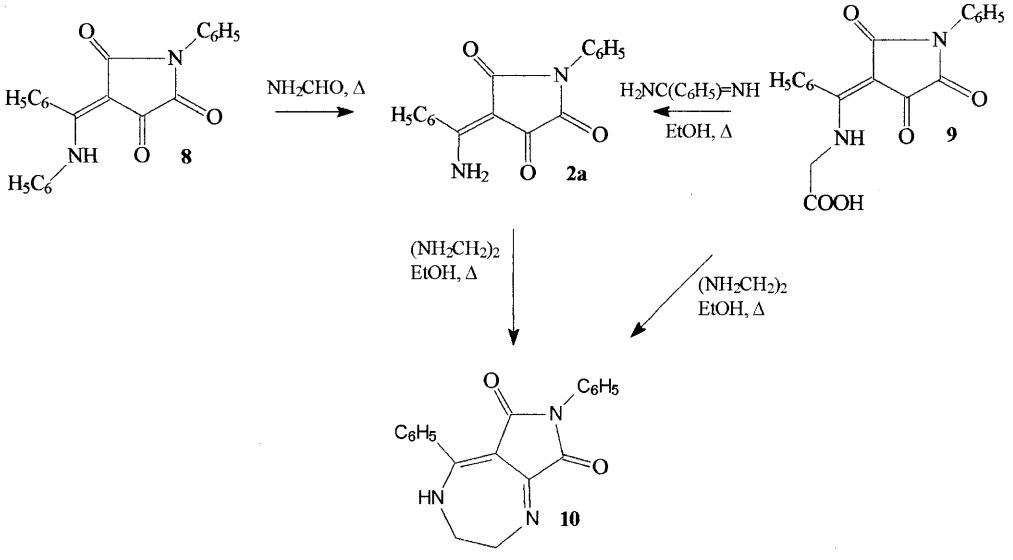
These results show that the condensation is followed by the decomposition of an amine and that high temperature favours both decomposition and formation of the cyclic product. Heating 4′-phenylmethylene-pyrrolidinetrione-1-semicarbazone (**6**) [15] in dowtherm led to pyrrolo[3,4-*c*]pyrazole derivative **7** [16], thus confirming the proposed mechanism (Scheme 3). The enaminone **2a** was also readily obtained, regardless of reaction temperature, by transamination of **8** and **9** with formamide and benzamidine, respectively (Scheme 4).

The β-aminoenone moiety could be efficiently reacted with a range of nucleophiles to afford the corresponding heterocyclic derivatives. Thus, **2a** and **7** underwent facile transamination to the pyrrolo[3,4-*e*]diazepine **10** [17]; it is a useful precursor to a variety of fused heterocyclic systems.

It is important to point out that it is possible to synthesize the enaminones of strong nitrogen bases by transamination which are hard to obtain by the formation of salts with polycarbonyls. No method of aminoenone synthesis based on the decomposition of urea, amidine, or semicarbazide derivatives could be found in the



Scheme 3



Scheme 4

literature. In the case of formamide, the reaction seems to be slightly more efficient. However, heating **2a** with formamidine in dowtherm effectively shortens the reaction time. Under these conditions, polycarbonyl compounds sensitive to *pH* can be safely converted to aminoenones because weak bases decompose to ammonia during heating. Moreover, products formed in dowtherm solution are easily precipitated by petroleum.

In conclusion, these procedures represent a convenient method for the efficient synthesis of β-aminoenones; what is more, the transamination extends their application to the formation of various heterocyclic systems.

Experimental

Melting points were determined on a Boetius PHMK 05 melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded in *DMSO*-d_6 and $CDCl_3$ with a Bruker AMX 500 NMR spectrometer using *TMS* as internal standard. The IR spectra were measured in Nujol and hexachlorobutadiene (*HCBN*) with a Bruker IFS 48 spectrometer. The EI mass spectra were obtained on an LKB 9000 S spectrometer and a Finnigan TSQ 700 triple quadruple mass spectrometer. Elemental analyses were carried out with an Eurovector analyser; their results were in good agreement with the calculated values.

1-Phenyl-4-(aminophenylmethylene)-pyrrolidine-2,3,5-trione (**2a**; $C_{17}H_{12}N_2O_3$)

i) A solution of 0.01 mol of **1a** in 10 cm^3 formamide was heated to 130°C for 4 h and cooled. The precipitate was filtered off and crystallized from *DMF*. Yield: 89%.

ii) To a solution of 0.01 mol of **1a** in 10 cm^3 dowtherm and 1 cm^3 acetic acid, 0.012 mol of formamidine acetate were added. The mixture was refluxed for 10 min. The aminoenone was precipitated with petroleum, filtered off, and crystallized from *DMF*. Yield: 73%.

iii) To a solution of 0.01 mol of **1a** in 10 cm^3 dowtherm and 1 cm^3 acetic acid, 0.012 mol of semicarbazide, thiosemicarbazide, urea, or thiourea were added. The mixture was refluxed for 2 min. The aminoenone was precipitated with petroleum, filtered off, and crystallized from *DMF*. Yields: 20, 15, 61, and 42%.

iv) To a solution of 0.01 mol of **1a** in 50 cm^3 EtOH, 0.012 mol of formamide were added. The solution was refluxed for 8 h and cooled. The precipitate was filtered and washed with boiling EtOH. The filtrate was left for crystallization (**3a**). The precipitate (**2a**) was crystallized from *DMF* or acetic acid. Yield: **2a**: 61%, **3a**: 11%.

v) A solution of 0.01 mol of **5a** in 10 cm^3 dowtherm was heated to 260°C for 2 min and cooled. The aminoenone was precipitated with petroleum, filtered off, and crystallized from *DMF*. Yield: 39%.

vi) To a solution of 0.01 mol of **8** in 50 cm^3 EtOH, or 10 cm^3 dowtherm, respectively, 0.012 mol of formamide were added. The solution was refluxed for 4 h and cooled. The precipitate was filtered and crystallized from *DMF*. Yields: 5, 20%.

vii) To a solution of 0.01 mol of **9** in 50 cm^3 EtOH, 0.012 mol of benzamidine hydrochloride were added. The solution was refluxed for 8 h and cooled. The precipitate was filtered and crystallized from *DMF*. Yield: 18%.

M.p.: 289°C; IR (*HCBN*): $\nu = 3374$, 3166 (NH), 3060 (C–H arom.), 1769, 1706 (C=O), 1612 (C=C arom.) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 500.13 MHz): 9.72 (2H, s, NH_2), 7.56–7.60 (3H, m, H arom.), 7.45–7.51 (4H, m, H arom.), 7.36–7.39 (3H, m, H arom.) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125.75 MHz): 167.45, 161.93, 132.047, 131.78, 131.49, 128.81, 128.58, 127.84, 127.69, 126.96, 79.13 ppm; MS: m/z (%) = 292 (26.2) [M^+], 264 (65.4) [M^+–CO]$^+$, 145 (100) [C_9H_7NO]$^+$.

1-Phenyl-4-(amino-4-chloro-phenylmethylene)-pyrrolidine-2,3,5-trione (**2b**; $C_{17}H_{11}N_2O_2Cl$)

A solution of 0.01 mol of **1b** in 10 cm^3 formamide was heated to 130°C for 4 h and cooled. The precipitate was filtered off and crystallized from *DMF*.

Yield: 87%; m.p.: 305°C; IR (*HCBN*): $\nu = 3395$, 3206 (NH), 3053 (C–H arom.), 1764, 1703 (C=O), 1602 (C=C arom.) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 500.13 MHz): 9.78 (2H, s, NH_2), 7.60 (2H, d, $J = 9$ Hz), 7.57 (2H, d, $J = 9$ Hz), 7.47 (2H, t, $J = 7$ Hz), 7.36 (3H, m) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125.75 MHz): 166.07, 161.93, 136.32, 131.76, 130.83, 128.64, 127.98, 127.77, 126.96 ppm; MS: m/z (%) = 328 (13.08) $[M+2]^+$, 326 (39.38) $[M^+]$, 298 (33.08) $[M^+–CO]$, 179 (100) $[^{35}ClC_6H_4NCO]^+$, 181 (33.08) $[^{37}ClC_6H_4NCO]^+$.

1-(4-Methylphenyl)-4-(aminophenylmethylene)-pyrrolidine-2,3,5-trione (**2c**; $C_{18}H_{14}N_2O_3$)

A solution of 0.01 mol of **1c** in 10 cm^3 formamide was heated to 130°C for 4 h and cooled. The precipitate was filtered off and crystallized from *DMF*.

Yield: 82%; m.p.: 272–274°C; IR (*HCBN*): $\nu = 3372$, 3172 (NH), 3035 (C–H arom.), 1764, 1701 (C=O), 1615 (C=C arom.) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 500.13 MHz): 9.71 (2H, s, NH_2), 7.59 (3H, t, $J = 7$ Hz), 7.5 (2H, t, $J = 8$ Hz), 7.27 (2H, d, $J = 8$ Hz), 7.23 (2H, d, $J = 8$ Hz), 2.34 (3H, s, CH_3) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125.75 MHz): 167.52, 162.16, 137.30, 132.14, 131.61, 129.24, 129.19, 128.92, 127.95, 126.84, 95.2, 20.78 ppm; MS: m/z (%) = 306 (29.56) $[M^+]$, 278 (63.24) $[M^+–CO]$, 133 (100) $[CH_3C_6H_4NCO]^+$.

2-(Hydroxyphenylmethylene)-3-oxo-N^1-phenylsuccinamide (**3a**; $C_{17}H_{13}N_2O_4$)

Yield: 11%; m.p.: 175°C; IR (*HCBN*): $\nu = 3171$ (NH), 3100–2600 (N–H bonded, C–H arom.), 1763, 1716 (C=O), 1633 (C=N), 1612 (N–H bending), 1601 (C=C arom.) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 500.13 MHz): 7.55–7.29 (10H, H arom.), 7.25 (1H, s, NH), 7.15 (1H, s, NH), 7.05 (1H, s, NH) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125.75 MHz): 186.95, 174.245, 170.21, 164.53, 141.21, 132.92, 129.89, 128.50, 128.38, 127.08, 126.81, 126.60, 97.88 ppm; MS: m/z (%) = 293 (10) $[M^+–NH_2]$, 265 (78.4) $[M^+–NH_2–CO]$, 105 (100) $[C_6H_5CO]^+$.

Salt of 4-(phenylhydroxymethylidene)-pyrrolidine-2,3,5-trione with formamidine (**4a**; $C_{18}H_{16}N_3O_4$)

To a solution of 0.01 mol of **1a** in 50 cm^3 EtOH, 0.012 mol of formamidine acetate were added. The solution was left overnight at room temperature. The precipitate was filtered off.

Yield: 65%; m.p.: 205°C; IR (*HCBN*): $\nu = 3500$–3000 (NH_2, NH_2^+), 1780, 1710, 1700 (C=O), 1660 (C=C arom.) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 500.13 MHz): 9.04 (2H, s, $=NH_2^+$), 8.71 (2H, s, NH_2), 7.87 (1H, s, CH), 7.54 (2H, d, $J = 7$ Hz), 7.37–7.45 (3H, m, H arom.), 7.29–7.35 (5H, m, H arom.) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125.75 MHz): 186.91, 174.27, 170.165, 164.58, 157.18, 141.38, 132.99, 129.74, 128.39, 127.01, 126.75, 126.48, 97.76 ppm; MS: m/z (%) = 293 (25) $[C_{17}H_{11}NO_4]^+$, 265 (26) $[M^+–NH_2CH{=}NH–CO]$, 105 (100) $[C_6H_5CO]^+$.

2-(Hydroxyphenylmethylene)-N^4-iminomethyl-3-oxo-N^1-phenylsuccinamide (**5a**; $C_{18}H_{16}N_3O_4$)

A solution of 0.01 mol of **4a** in 50 cm^3 EtOH was refluxed for 30 min and cooled. The precipitate was filtered off and crystallized from EtOH.

Yield: 43%; m.p.: 154°C; IR (*HCBN*): $\nu = 3280$, 3200 (NH), 3070 (C–H arom.), 1750, 1720, 1708 (C=O), 1600 (C=C arom.) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, δ, 500.13 MHz): 8.07 (3H, br s, 2NH, OH), 7.88 (1H, s, CH), 7.55 (2H, d, $J = 8$ Hz), 738–7.46 (4H, m, 3H arom., NH), 7.29–7.35 (5H, m,

H arom.) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125.75 MHz): 187.03, 174.38, 170.24, 164.57, 157.21, 141.32, 132.96, 129.80, 128.40, 128.29, 127.03, 126.77, 126.53, 97.82 ppm; MS: m/z (%) = 293 (10) [M^+–NH_2CH=NH], 265 (26) [M^+–NH_2CH=NH–CO], 105 (100) $[C_6H_5CO]^+$.

3,5-Diphenylpyrrolo[3,4-c]pyrazole-4,6(1H)-dione (**7**; $C_{17}H_{11}N_2O_2$; [16])

A solution of 0.01 mol of **6** in 10 cm^3 dowtherm was heated to 260°C for 1 h and cooled. The pyrrolo[3,4-*c*]pyrazole was precipitated with petroleum, filtered off, and crystallized from EtOH.

Yield: 43%; m.p.: 259–261°C; ^{1}H NMR (*DMSO*-d_6, δ, 500.13 MHz): 14.79 (1H, br s, NH), 8.19 (2H, d, J = 8.6 Hz), 7.59 (2H, t, J = 7.2 Hz), 7.55–7.51 (3H, m, 3H arom.), 7.45–7.42 (3H, m, H arom.) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 125.75 MHz): 161.44, 161.15, 152.20, 141.05, 132.22, 130.59, 129.27, 128.68, 127.90, 127.62, 126.62, 126.25, 114.56.

5,7-Diphenylpyrrolo[3,4-e][1,4]diazepine-6,8(4H,8H)-dione (**10**; $C_{19}H_{15}N_3O_2$; [17])

To a solution of 0.01 mol of **2a** or **9** in 50 cm^3 EtOH, 0.012 mol of ethylenediamine were added. The solution was refluxed for 2 h and cooled. The precipitate was filtered and crystallized from *DMF*/H_2O. Yields: 72, 39%.

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