Studies on Isocyanides and Related Compounds: A Novel Synthesis of Pyrroles via Ugi Reaction

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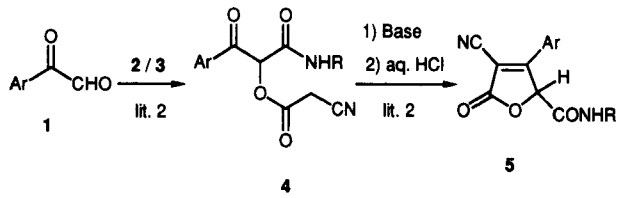
A series of *N*-substituted 1,3-diaryl-4-cyano-2,5-dihydro-5-oxopyrrole-2-carboxamides **9** is obtained by reacting arylglyoxal anils **6** with isocyanides **3** and cyanoacetic acid (**2**). Compounds **9** react quickly with diazomethane to give *N*-substituted 1,3-diaryl-4-cyano-5-methoxypyrrole-2-carboxamides **12**.

In continuation of our studies on the synthesis of heterocyclic compounds from isocyanides[1] we have described a novel synthesis of furan derivatives[2] based on the Passerini reaction between arylglyoxals **1**, cyanoacetic acid (**2**), and isocyanides **3**. This reaction affords *N*-substituted 3-aryl-2-cyanoacetoxy-3-oxopropionamides **4** which are cyclized to *N*-substituted 3-aryl-4-cyano-2,5-dihydro-5-oxofuran-2-carboxamides **5**.



Scheme 1

In order to evaluate the possibility of extending this method to the preparation of pyrrole derivatives, we have attempted to perform the above reactions by employing arylglyoxal anils **6** in the place of arylglyoxals **1**.

The first step of this synthesis consists of the preparation of the arylglyoxals anils **6** by refluxing freshly prepared arylglyoxals **1** with amines **7** in toluene, while the water

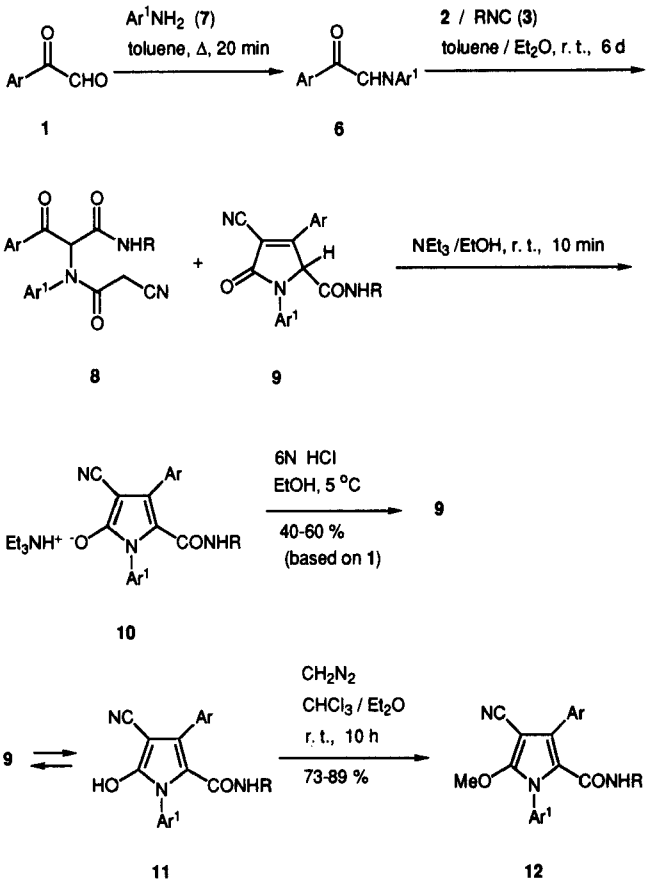


Table 1. Compounds **9a–h** Prepared

Product[a]	Yield (%)[b,c]	mp (°C) (solvent)	IR (KBr) ν (cm⁻¹)
9a	42	220–223 (EtOH/DMF)	3413 (NH), 2232 (CN), 1693 (CO), 1660 (CO)
9b	48	204–206 (EtOH/DMF)	3303 (NH), 2227 (CN), 1721 (CO), 1651 (CO)
9c	51	256–258 (EtOH/DMF)	3290 (NH), 2232 (CN), 1711 (CO), 1652 (CO)
9d	57	253–255 (EtOH/DMF)	3293 (NH), 2228 (CN), 1703 (CO), 1649 (CO)
9e	55	215–217 (EtOH/DMF)	3286 (NH), 2227 (CN), 1708 (CO), 1645 (CO)
9f	60	235–236 (EtOH/DMF)	3285 (NH), 2228 (CN), 1710 (CO), 1645 (CO)
9g	40	155–159 (EtOH)	3313 (NH), 2231 (CN), 1708 (CO), 1657 (CO)
9h	43	222–223 (EtOH)	3289 (NH), 2230 (CN), 1705 (CO), 1656 (CO)

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.24, N ±0.20.
[b] Yield of pure isolated product.
[c] Based on **1**.

1	Ar
a	C_6H_5
b	4-ClC_6H_4

3	R
a	c-C_6H_{11}
b	n-C_6H_{13}

7	Ar^1
a	C_6H_5
b	3-ClC_6H_4
c	4-ClC_6H_4
d	4-$CH_3C_6H_4$

6	Ar	Ar^1
a	C_6H_5	C_6H_5
b	C_6H_5	3-ClC_6H_4
c	C_6H_5	4-ClC_6H_4
d	C_6H_5	4-$CH_3C_6H_4$
e	4-ClC_6H_4	C_6H_5
f	4-ClC_6H_4	4-ClC_6H_4

8, 9, 10, 11, 12	Ar	Ar^1	R
a	C_6H_5	C_6H_5	c-C_6H_{11}
b	C_6H_5	3-ClC_6H_4	c-C_6H_{11}
c	C_6H_5	4-ClC_6H_4	c-C_6H_{11}
d	C_6H_5	4-$CH_3C_6H_4$	c-C_6H_{11}
e	4-ClC_6H_4	C_6H_5	c-C_6H_{11}
f	4-ClC_6H_4	4-ClC_6H_4	c-C_6H_{11}
g	4-ClC_6H_4	C_6H_5	n-C_6H_{13}
h	4-ClC_6H_4	4-ClC_6H_4	n-C_6H_{13}

Scheme 2

Table 2. Compounds **12a–h** Prepared

Product[a]	Yield (%)[b]	mp (°C) (solvent)	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
12a	83	235–238 (EtOH)	3275 (NH), 2225 (CN), 1632 (CO)	0.70–1.61 (m, $10H_{cyclohexane}$), 3.52–3.67 (m, 1H, $1\text{-}H_{cyclohexane}$), 4.19 (s, 3H, OCH_3), 5.20 (d, 1H, J = 8.4, NH), 7.26–7.51 (m, $10H_{arom}$)
12b	89	249–251 (EtOH)	3259 (NH), 2220 (CN), 1630 (CO)	0.71–1.73 (m, $10H_{cyclohexane}$), 3.60–3.77 (m, 1H, $1\text{-}H_{cyclohexane}$), 4.21 (s, 3H, OCH_3), 5.23 (d, 1H, J = 7.6, NH), 7.17–7.51 (m, $9H_{arom}$)
12c	83	255–257 (EtOH)	3260 (NH), 2221 (CN), 1630 (CO)	0.69–1.61 (m, $10H_{cyclohexane}$), 3.50–3.66 (m, 1H, $1\text{-}H_{cyclohexane}$), 4.20 (s, 3H, OCH_3), 5.22 (d, 1H, J = 8.3, NH), 7.20–7.47 (m, $9H_{arom}$)
12d	80	227–230 (EtOH)	3250 (NH), 2217 (CN), 1630 (CO)	0.69–1.73 (m, $10H_{arom}$), 2.44 (s, 3H, CH_3), 3.52–3.67 (m, 1H, $1\text{-}H_{cyclohexane}$), 4.19 (s, 3H, OCH_3), 5.20 (d, 1H, J = 7.7, NH), 7.15–7.50 (m, $9H_{arom}$)
12e	81	206–209 (*i*-PrOH)	3296 (NH), 2220 (CN), 1640 (CO)	0.73–1.63 (m, $10H_{cyclohexane}$), 3.53–3.68 (m, 1H, $1\text{-}H_{cyclohexane}$), 4.19 (s, 3H, OCH_3), 5.15 (d, 1H, J = 7.6, NH), 7.26–7.48 (m, $9H_{arom}$)
12f	81	218–219 (*i*-PrOH)	3302 (NH), 2215 (CN), 1639 (CO)	0.69–1.64 (m, $10H_{cyclohexane}$), 3.52–3.68 (m, 1H, $1\text{-}H_{cyclohexane}$), 4.19 (s, 3H, OCH_3), 5.20 (d, 1H, J = 8.3, NH), 7.16–7.49 (m, $8H_{arom}$)
12g	73	115–118 (*i*-PrOH)	3329 (NH), 2217 (CN), 1644 (CO)	0.81–1.26 (m, $11H_{hexane}$), 3.00–3.10 (m, 2H, $NHCH_2$), 4.19 (s, 3H, OCH_3), 5.23–5.35 (m, 1H, NH), 7.25–7.50 (m, $9H_{arom}$)
12h	76	138–141 (*i*-PrOH)	3299 (NH), 2215 (CN), 1643 (CO)	0.82–1.28 (m, $11H_{hexane}$), 3.01–3.11 (m, 2H, $NHCH_2$), 4.20 (s, 3H, OCH_3), 5.25–5.36 (m, 1H, NH), 7.19–7.49 (m, $8H_{arom}$)

[a] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.23, N ± 0.25. [b] Yield of pure isolated product.

formed during condensation is continuously removed by means of a Dean–Stark apparatus. Attempts to isolate the anils **6** in a pure form either by distillation or chromatographic methods were unsuccessful, confirming the results of a previous work.[3]

The reaction between arylglyoxals **1**, cyanoacetic acid **(2)**, and isocyanides **3** takes place quickly; in contrast, the reaction between arylglyoxal anils **6**, cyanoacetic acid **(2)**, and isocyanides **3** is slow. After 24 h at room temperature compounds **8a,b** are obtained in very low yields. By employing longer reaction periods the yields of **8** increase, but a mixture of **8** and **9** is always found, owing to the high tendency of compounds **8** to cyclize, even in the absence of a base. Upon treatment of the reaction mixture with triethylamine, a solution of the olates **10**, arising from the base-induced cyclization of **8** and the deprotonation of **9**, is obtained. Upon treatment of this solution with aqueous hydrochloric acid, *N*-substituted 1,3-diaryl-4-cyano-2,5-dihydro-5-oxopyrrole-2-carboxamides **9** are obtained in fair yields.

Compounds **9** react very quickly with diazomethane to give *N*-substituted 1,3-diaryl-4-cyano-5-methoxypyrrole-2-carboxamides **12** in high yields. This may be explained on the basis of the high acidity of the OH group of the tautomers **11**.[4]

Mps were determined using a Büchi 512 melting point apparatus and are uncorrected. ^1H NMR spectra were obtained using a Varian Gemini 200 spectrometer. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer. Microanalyses were obtained using a Perkin-Elmer 240 elemental analyzer. Isocyanide **3a** is commercially available. Isocyanide **3b**[5] and arylglyoxals **1a**[6] and **1b**[7] were prepared following literature procedures. Compunds **8a,b** gave correct microanalyses: C ± 0.31, H ± 0.23, N ± 0.22.

N-Substituted 1,3-Diaryl-4-cyano-2,5-dihydro-5-oxopyrrole-2-carboxamides 9; General Procedure:

A solution of **1** (22 mmol) and **7** (22 mmol) in toluene (120 mL) was refluxed for 20 min in a Dean–Stark apparatus. The resulting solution of the crude **6** was evaporated to ca. 10 mL under reduced pressure and then treated with a saturated solution of **2** (2.15 g, 25.3 mmol) in Et_2O and a solution of **3** (22 mmol) in Et_2O (10 mL). The resulting mixture was allowed to react at r.t. for 6 d and then evaporated to dryness. The residue was stirred with EtOH (40 mL) and the resulting suspension was treated dropwise with NEt_3 (2.56 g, 25.3 mmol). The resulting solution was stirred for 10 min at r.t., then cooled at 5 °C and treated dropwise with 6 N HCl until pH = 4. The resulting suspension was filtered to give **9**.

N-Substituted 2-(N-Aryl-N-cyanoacetyl)amino-3-oxo-3-phenylpropionamides 8; General Procedure:

These products were obtained by reacting the crude anils **6a,b** with **2** and **3a** as described for the preparation of compounds **9**, except that the reaction mixture was filtered after 24 h at r.t. The collected products were washed with Et_2O, then with EtOH and Et_2O again. Attempts to increase the purity of **8** by recrystallization failed since a partial cyclization took place.

2-(N-Cyanoacetyl-N-phenyl)amino-N-cyclohexyl-3-oxo-3-phenylpropionamide **(8a)**;

Yield: 0.71 g (8%); mp 138–141 °C.

IR (KBr): ν = 3300, 1678, 1649 cm^{-1}.

2-[N-(3-Chlorophenyl)-N-cyanoacetyl]amino-N-cyclohexyl-3-oxo-3-phenylpropionamide **(8b)**:

Yield: 1.06 g (11%); mp 140–143 °C.

IR (KBr): ν = 3295, 1679, 1645 cm^{-1}.

N-Substituted 1,3-Diaryl-4-cyano-5-methoxypyrrole-2-carboxamides 12; General Procedure:

A saturated solution of **9** (2.5 mmol) in $CHCl_3$ was treated with a large excess of CH_2N_2 in Et_2O and allowed to react at r.t. for 10 h. The resulting solution was evaporated to dryness and the residue was recrystallized from a suitable solvent.

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