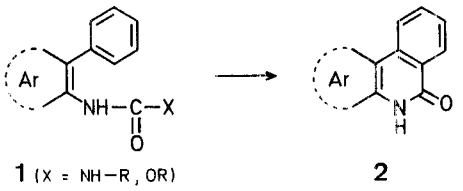
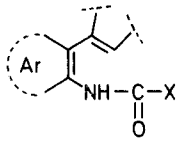
[c] Conditions: DMSO-d_6/TMS_{int}.
[d] $J_{CH_{(w)},CH_{2(x)}} = 6.5$ Hz.



1 (X = NH—R, OR) 2

Scheme A

Assuming that substitution of the benzene ring β to the amine with an isolated double bond **(3)** should greatly facilitate this type of cyclization reaction, we prepared a number of 5-amino-4-cycloalkenylpyrazoles **(4)** and -isoxazoles **(8)**[1].



3

We describe here the high yield, direct synthesis of different pyrazolo[3,4-*b*]pyridones **7** and isoxazolo[5,4-*b*]pyridones **10** under mild conditions from amines **4** and **8**, respectively (Schemes **B** and **C**, Methods B and C).

For the synthesis of the ring-fused isoquinolones of the type **7** we initially used our earlier described[6,7] Method A: the phenylureas **5a, b, f** were heated at their melting points (~ 200–220 °C) for a few minutes whereupon evolution of aniline was observed and the pure products **7a, b, f** could be isolated in nearly quantitative yield by recrystallization of the solid residue. In an attempt to avoid the isolation of the ureas **5**, a number of amines **4**[1] were treated with ethyl or phenyl isocyanate in refluxing xylene but no pyridone **7** was isolated even after several hours. Surprisingly, using ethyl isocyanate in a basic solvent like 4-methylpyridine or even pyridine at reflux temperatures (Method B), the reaction **4** → **7** proceeded readily and with good yields. Three to seven

Easy Synthesis of New Ring-Fused Pyridones from Heteroaromatic β-Vinylamines[1]

G. Winters, A. Sala, A. de Paoli, V. Ferri

Research Laboratories of DOW-Lepetit, I-20158 Milano, Italy

Aromatic isocyanates, generally prepared via Curtius rearrangement of acyl azides, are known to undergo cyclization reactions to 2-pyridone derivatives during photolysis[2], heating in the presence of aluminum chloride[3], and even spontaneously[4]. Aromatic and heteroaromatic amine derivatives such as carbamates **1** (X = OR) and ureas **1** (X = NH—R), precursors of isocyanates, have been cyclized thermally to isoquinolones **2**[5,6,7] (Scheme A).

Table 1. Ring-Fused Pyridones **7** prepared

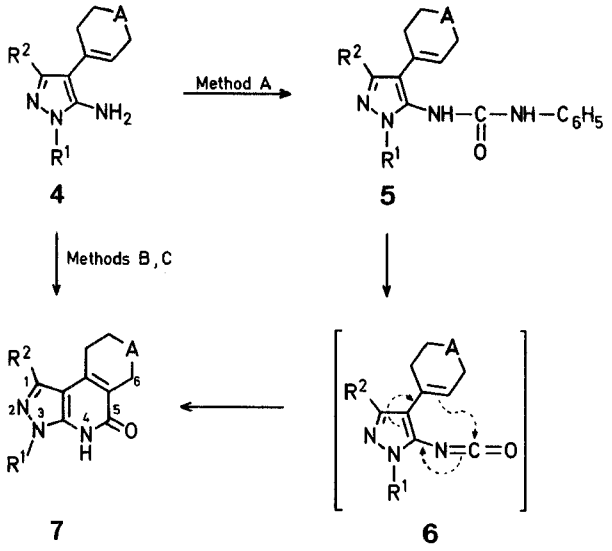
7	R^1	R^2	A	Method	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]
a	CH_3	CH_3	–	A	94	305° (DMF)	$C_{11}H_{13}N_3O$ (203.25)
b	CH_3	CH_3	CH_2	A	98	>300° (DMF)	$C_{12}H_{15}N_3O$ (217.3)
c	CH_3	CH_3	CH_2—CH_2	B	75	272–273° (methanol)	$C_{13}H_{17}N_3O$ (231.3)
d	CH_3	CH_3	$N(COCH_3)$	B	80	>300° (4-methylpyridine)	$C_{13}H_{16}N_4O_2$ (260.3)
e	CH_3	CH_3	$N(CH_3)$	B	86	294–297° (4-methylpyridine)	$C_{12}H_{16}N_4O$ (232.3)
				C	79		
f	C_6H_5	C_6H_5	CH_2	A	85	228–229° (DMF)	$C_{22}H_{19}N_3O$ (341.4)

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.10, N ±0.18.

Table 2. Ring-Fused Pyridones **10** prepared

10	R	A	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]
a	CH_3	CH_2	88	255° (DMF/methanol)	$C_{11}H_{12}N_2O_2$ (204.2)
b	CH_3	CH_2—CH_2	67	226–227° (methanol)	$C_{12}H_{14}N_2O_2$ (218.25)
c	CH_3	$N(CH_3)$	83	270° (dec.) (H_2O)	$C_{11}H_{13}N_3O_2 \cdot HCl$ (255.7)
d	CH_3	$N(COCH_3)$	83	259–261° (DMF)	$C_{12}H_{13}N_3O_3$ (247.3)
e	C_6H_5	–	81	230° (dec.) (DMF)	$C_{15}H_{12}N_2O_2$ (252.3)
f	C_6H_5	CH_2	82	228–229° (DMF/methanol)	$C_{16}H_{14}N_2O_2$ (266.3)

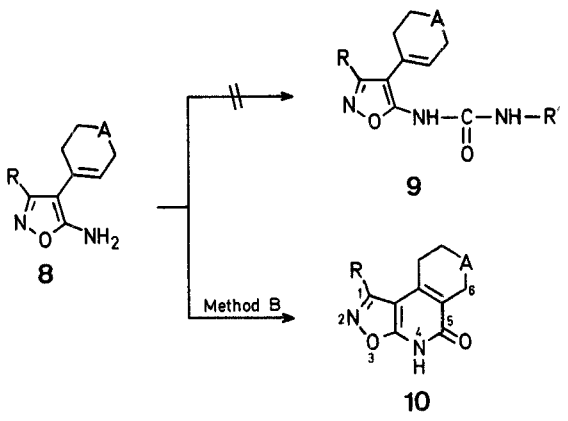
[a] Satisfactory microanalyses obtained: C ±0.16, H ±0.13, N ±0.15



Scheme **B**

hours heating were necessary depending on the solvent. In one case, in which a basic N-atom was present in the molecule (**4e**)[1], the autocatalyzed reaction proceeded even in xylene (Method C).

The 5-amino-4-cycloalkenylisoxazoles **8**[1] behaved quite differently since we were unable to obtain the corresponding ureas **9** using ethyl or phenyl isocyanate in boiling ethyl acetate, toluene, or xylene (Scheme **C**), only starting material being recovered. However, when excess ethyl isocyanate in refluxing pyridine was used, the rather insoluble pyridones **10** could be directly isolated in good yields (Table 2).



Scheme **C**

The pyridone derivatives **7** and **10** as well as the ureas **8** were fully characterized by microanalysis, I.R., and ^{1}H-N.M.R. spectrometry.

4-(1-Cyclopentenyl)-1,3-dimethyl-5-[(phenylaminocarbonyl)-amino]-pyrazole (5a); Typical procedure:

Phenyl isocyanate (1.1 g, 9.23 mmol) is added to a stirred solution of 5-amino-4-(1-cyclopentenyl)-1,3-dimethylpyrazole[1] (**4a**; 1.4 g, 7.9 mmol) in benzene (30 ml) and stirring is continued for 3 h at room temperature. The resultant suspension is refluxed for 15 min, then cooled. The solid product is isolated by suction and washed with ether to give practically pure **5a** (as checked by T.L.C.); yield: 2.11 g (89%). Analytically pure **5a** is obtained by recrystallization from ethyl acetate; m.p. 209°C (dec.)[8].

$C_{17}H_{20}N_4O$	calc.	C 68.98	H 6.80	N 18.91
(296.4)	found	68.65	6.91	18.76

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ = 2.16 (s, C—CH_3); 3.63 (s, N—CH_3); 5.59 (m, =CH—); 6.8–7.4 (m, C_6H_5); 7.55–8.0 ppm (2br. s, NH).

Table 3. ^{1}H-N.M.R. (DMSO-d_6/TMS_{int}) Data of Compounds **7**[a] and **10**[a]; δ [ppm]

Product	R^1	R^2	NH	A	$CH_{2(x)}$	$CH_{2(y)}$	$CH_{2(z)}$
7a[b]	4.25 (s)	2.81 (s)	exchanged		2.8–3.6 (m)	2.1–2.7 (m)	2.8–3.6 (m)
7b[b]	4.23 (s)	2.87 (s)	exchanged	1.7–2.3 (m)	2.9–3.3 (m)	1.7–2.3 (m)	2.5–2.8 (m)
7c	3.81 (s)	2.45 (s)	11.4–12.2 (br.s)	1.2–2.0 (m)	2.6–3.2 (m)	1.2–2.0 (m)	2.6–3.2 (m)
7d[b]	4.29 (s)	2.90 (s)	exchanged	2.7 (s)	4.85 (m)	4.23 (m)	3.42 (m)
7e[c]	3.97 (s)	2.45 (s)	11.0–11.8 (br.s)	2.5 (s)	3.4 (m)	3.0 (m)	2.70 (m)
7f[c]	7.1–7.8 (m)	7.1–8.0 (m)	10.3–12.3 (br.s)	1.4–2.0 (m)	2.4–2.7 (m)	1.4–2.0 (m)	2.4–2.7 (m)
	R						
10a	2.51 (s)		10.8–12.2 (br.s)	1.6–1.9 (m)	2.8–3.2 (m)	1.6–1.9 (m)	2.3–2.6 (m)
10b	2.52 (s)		11.7–12.4 (br.s)	1.2–2.2 (m)	2.7–3.2 (m)	1.2–2.2 (m)	2.7–3.2 (m)
10c	2.58 (s)		11.2–12.3 (br.s)	2.97 (s)	4.15 (m)	3.51 (m)	3.36 (m)
10d	2.53 (s)		11.6–13.2 (br.s)	2.15 (s)	4.46 (m)	3.80 (m)	3.3–3.8 (m)
10e	7.6–7.9 (m)		11.8–12.8 (br.s)		2.6–3.2 (m)	1.7–2.3 (m)	2.6–3.2 (m)
10f	7.8–8.0 (m)		10.2–11.4 (br.s)	1.3–2.0 (m)	2.2–2.9 (m)	1.3–2.0 (m)	2.2–2.9 (m)

[a] Numbering of cycloalkenyl protons: 

[b] Conditions: F_3C—COOD/TMS_{int}.

[c] Conditions: $CDCl_3$/TMS_{int}.

4-(1-Cyclohexenyl)-1,3-dimethyl-5-[(phenylaminocarbonyl)-amino]-pyrazole (5b):

This compound is prepared in an analogous manner; yield: 92%; m.p. 203°C (dec.)[8].

$C_{18}H_{22}N_4O$ (310.41) calc. C 69.65 H 7.14 N 18.05
found 69.85 7.22 18.13

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ = 2.20 (s, C—CH_3; 3.57 (s, N—CH_3; 5.77 (m, =CH—); 6.7–7.6 (m, C_6H_5); 7.98–8.84 ppm (2b, NH).

4-(1-Cyclohexenyl-1,3-diphenyl-5-[(phenylaminocarbonyl)-amino]-pyrazole (5c):

This compound is prepared in an analogous manner; yield: 85%; m.p. 200–202°C (dec.)[8].

$C_{28}H_{26}N_4O$ (434.55) calc. C 77.39 H 6.03 N 12.90
found 77.52 6.05 12.78

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ = 5.82 (m, =CH—); 6.8–8.0 (m, 3 C_6H_5); 7.69–8.30 ppm (2b, NH).

1,3-Dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocyclopenta[*d*]pyrazolo-[3,4-*b*]pyridine (7a); Typical Procedure:

Method A: The crude urea derivative **5a** (1.2 g, 4.05 mmol) is heated at ~ 210°C (oil bath) for 5 min; aniline distils off. The residue is cooled, washed free from aniline with ether, and crystallized from dimethylformamide to give pure **7a**; yield: 0.77 g (94%); m.p. 305°C.

1,3,7-Trimethyl-5-oxo-4,5,6,7,8,9-hexahydro-3*H*-pyrazolo[3,4-*c*]-[2,7]naphthyridine (7e); Typical Procedures:

Method B: Ethyl isocyanate (2.37 ml, 30 mmol) is added to a stirred solution of 5-amino-1,3-dimethyl-4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-pyrazole[1] (**4e**; 2.06 g, 10 mmol) in 4-methylpyridine (20 ml). The mixture is refluxed for 3 h, then cooled in ice water. The solid product is isolated by suction and washed thoroughly with ethyl acetate to give pure **7e**; yield: 2.0 g (86%); m.p. 294–297°C.

When pyridine is used in place of 4-methylpyridine, the mixture is refluxed for 7 h; yield: 73%.

Method C: Ethyl isocyanate (7.11 ml, 90 mmol) is added to a stirred solution of 5-amino-1,3-dimethyl-4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-pyrazole[1] (**4e**; 6.19 g, 30 mmol) in xylene (60 ml). The mixture is refluxed for 4 h, then cooled in ice water. The solid product is isolated by suction and washed thoroughly with ether; yield of pure **7e**: 5.5 g (79%); m.p. 294–297°C.

1-Methyl-5-oxo-4,5,6,7,8,9-hexahydroisoxazolo[5,4-*c*]isoquinoline (10a); Typical Procedure:

A mixture of 5-amino-4-(1-cyclohexenyl)-3-methylisoxazole (**8a**; 9.5 g, 50 mmol) and ethyl isocyanate (11.9 ml, 150 mmol) in pyridine (95 ml) is refluxed for 3 h. The solvent is removed under reduced pressure; the residue is triturated with hot ethyl acetate, then cooled, and the pure product **10a** isolated by suction; yield: 9.0 g (88%). Analytically pure **10a** is obtained by recrystallization from dimethylformamide/methanol; m.p. 255°C.

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[8] During melting point determinations, compounds **5** are transformed to **7**.