Studies on Pyrrolidinones. On the Carbamoylation of Some Pyroglutamic Derivatives

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The carbamoylation of some lactams derivatived from pyroglutamic acid as been studied; better yields were obtained starting from the unsubstitued lactam (toluene, 80°) rather than starting with the *N*-silyl-lactam (room temperature), although these latter reaction conditions could be interesting for heat sensitive compounds. Methyl and phenyl isothiocyanate react only with the sodium salt of methyl pyroglutamate, giving 1,5-diaddition products.

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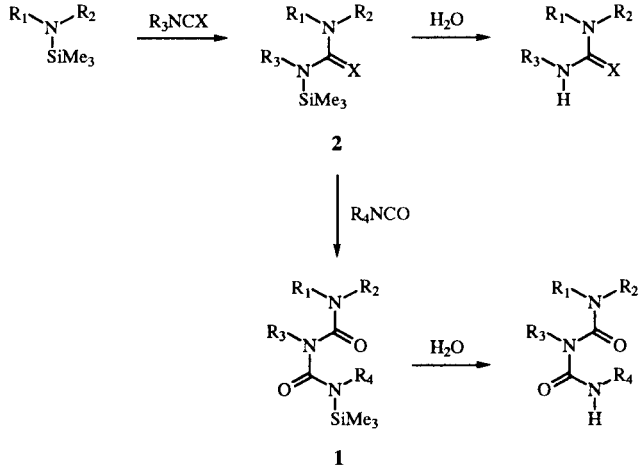
N-Carbamoyllactams are reported to show a broad spectrum of biological activities. Some of these compounds have been shown to exhibit bactericidal [1], herbicidal [2] or other agrochemical properties [3], or possess interesting pharmaceutical properties [4]. These observations and our interest in heterocycles derived from lactams prompted us to study the *N*-carbamoylation of pyrrolidinone, of pyroglutamic esters and of new structures we recently synthesized [5].

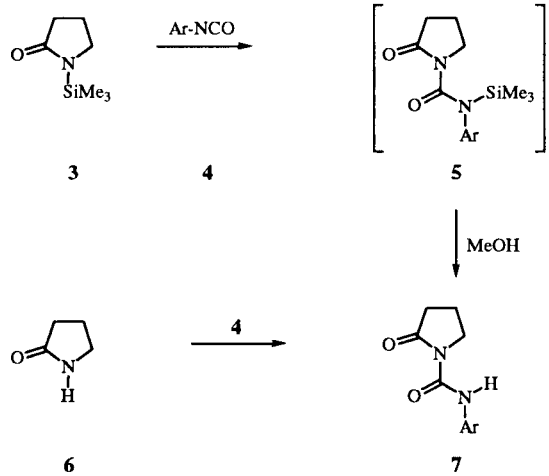
It is well known that the best acylation method for lactams is to react an acyl chloride with the *N*-silyllactam [6], and that isocyanates reacts easily with lactams to give *N*-carbamoyl derivatives. This reaction can be performed without solvent at high temperature, giving a low yield [4] or in toluene or dioxane, giving high yields after refluxing for some hours [1,7]. On the other hand, while to our knowledge the reaction of silyllactams with isocyanates has not been studied, *N*-silylamines react with iso (thio) cyanates to give a high yield of *N*-silylureas **2**; compounds **2** can then react again by inserting a second isocyanate molecule, yielding products such as **1** [8] (Scheme 1).

N-Trimethylsilylpyrrolidone **3** was first reacted with aryl isocyanates **4** under various conditions (1-3 equivalents of isocyanate, room temperature or 80°, no catalyst or F^- or triflic acid as catalyst, no solvent or in methylene dichloride...). In all the cases, only the insertion of a single isocyanate molecule into the *N*-Si bond was observed, giving medium to good yields of products **7** (room temperature). However this reaction often gives complex mixtures

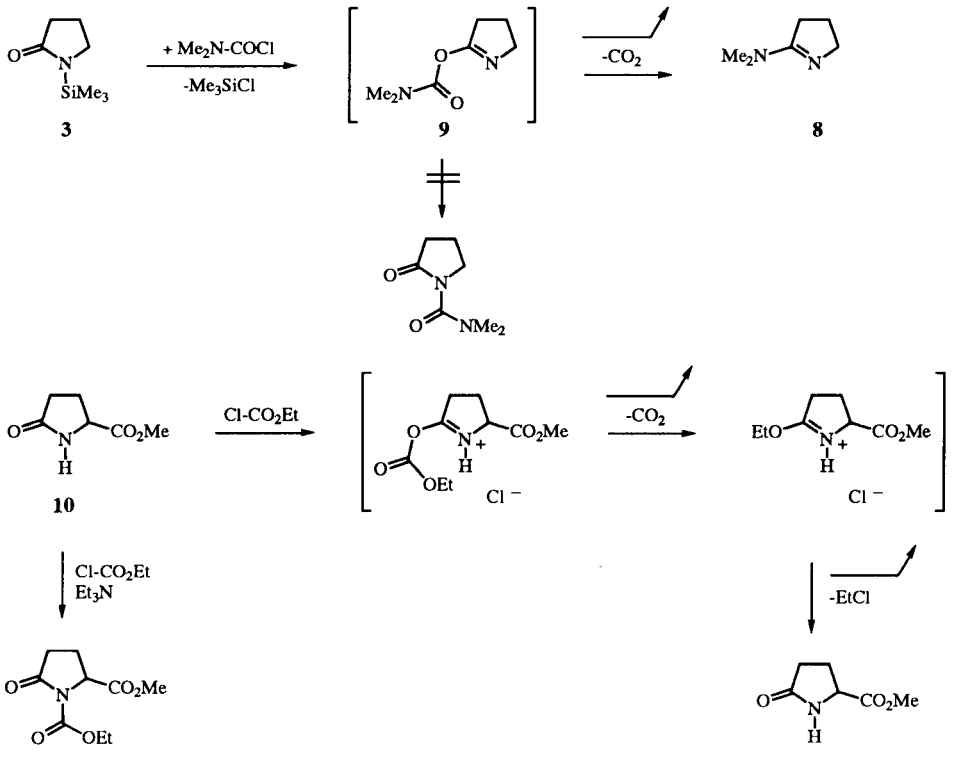
Scheme 1



Scheme 2



Scheme 3



due to the formation of dimers and trimers of the isocyanate. It is interesting to hydrolise the trimethylsilyl group of intermediate **5** with methanol because isocyanate excess gives then a methyl arylcarbamate which is easy to remove. We also performed the reaction starting from *N*-unsubstituted pyrrolidone **6** in toluene at 80° [1,7]. In fact, in this last case, good yields are also obtained and the purification of products **7** is easier (Scheme 2). In conclusion, it is more interesting to start from the unsubstitued lactam (toluene, 80°) rather than to utilise the *N*-silyllactam (room temperature), although these latter reaction conditions could be used for heat sensitive compounds.

It was also tried to obtain a *N*-disubstituted carbamate starting from dimethylcarbamyl chloride, but with *N*-trimethylsilyl pyrrolidone **3**, as well as with pyrrolidone **6** [9] amidine **8** was obtained, because an unstable carbamoyl iminoether **9** was formed as an intermediate. The addition of triethylamine allows to avoid the formation of this intermediate in the case of methyl pyroglutamate **10** and ethyl chloroformate [6b], but did not avoid the formation of **8** (Scheme 3).

The condensation of isocyanate was then accomplished with methyl pyroglutamate **10**, with the oxadiazolylpyrrolidone **11** and with the triazinone **12** [5]. Likewise their *N*-trimethylsilyl compounds **13**, **14** and **15** also react with isocyanates. In all cases better yields of **16**, **17** and **18** were obtained starting from the unsubstitued lactam (toluene, 80°) than starting with the *N*-silyllactam (room temperature).

An intersting observation was made during a methanol recrystallization attempt of compound **18c** (R' = 3,4-dichlorophenyl). Methanol opens the triazinone ring giving the pyroglutamic ester **19**, and addition of deuterated sodium hydroxide into the nmr tube recyclizes this ester to the initial triazine **18** (Scheme 5).

Some attempts were also made to react isothiocyanate with pyroglutamic esters **10** and **13**, but even in the

Scheme 4

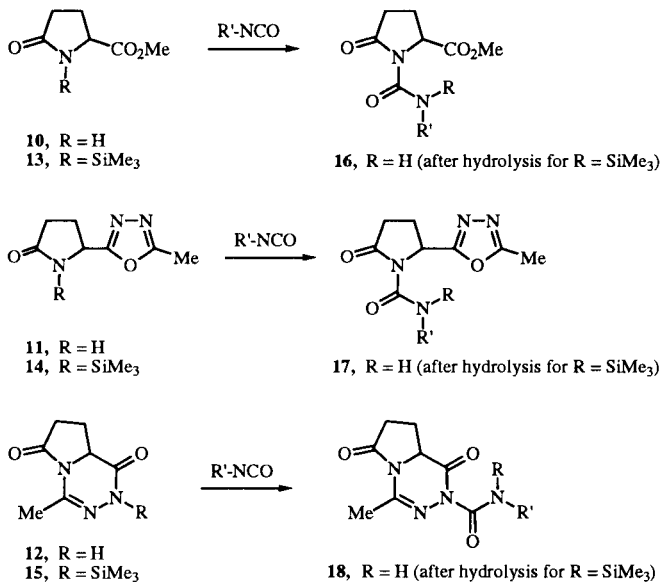


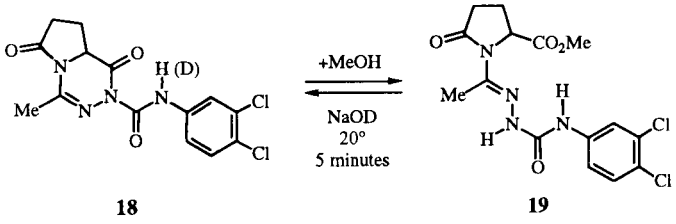
Table 1

Physical Properties of New Compounds

No.	R'	Mp °C (Solvent)	IR (nujol) ν cm^{-1}	^1H NMR ($CDCl_3$)
16a	*n*-Bu	52 (hexane)	1675, 1715, 1740 (C=O), 3290 (N-H)	0.7-1.75 (m, 7 H), 1.9-2.9 (m, 4 H), 3-3.5 (m, 2 H), 3.78 (s, 3 H), 4.6-4.95 (m, 1 H), 8-8.5 [a] (m, 1 H)
16b	*t*-Bu	82 (hexane)	1680, 1715, 1735 (C=O), 3290 (N-H)	1.36 (s, 9 H), 1.75-2.9 (m, 4 H), 3.78 (s, 3 H), 4.55-4.9 (m, 1 H), 7.95-8.4 [a] (m, 1 H)
16c	Ph	135 (methanol)	1445, 1550, 1590 (C=C arom), 1690, 1710, 1740 (C=O), 3220 (N-H)	1.9-3 (m, 4 H), 3.78 (s, 3 H), 4.7-5 (m, 1 H), 6.9-7.8 (m, 5 H), 10.3-10.6 [a] (m, 1 H)
16d	*p*-Cl-Ph	170 (methanol)	1490, 1560, 1600 (C=C arom), 1675, 1720, 1745 (C=O), 3140 (N-H)	1.9-3 (m 4 H), 3.78 (s, 3 H), 4.7-5.05 (m, 1 H), 7.1-7.65 (m, 4 H), 10.2-10.6 [a] (m, 1 H)
16e	*m,p*-Cl_2-Ph	171 (methanol)	1475, 1540, 1580 (C=C arom), 1680, 1715, 1730 (C=O), 3160 (N-H)	1.95-3 (m, 4 H), 3.82 (s, 3 H), 4.7-5 (m, 1 H), 7.2-7.4 (m, 2 H), 7.7-7.8 (m, 1 H), 10.35-10.7 [a] (m, 1 H)
16f	*m*-CF_3-Ph	83 (methanol)	1490, 1565, 1610 (C=C arom), 1680, 1725, 1750 (C=O), 3180 (N-H)	1.9-3 (m, 4 H), 3.81 (s, 3 H), 4.7-5.1 (m, 1 H), 7-8 (m, 4 H), 9.6-10 [a] (m, 1 H)
17a	*n*-Bu	45 (pentane)	1690, 1710 (C=O), 1585 (C=N), 3290 (N-H)	0.6-1.85 (m, 7 H), 1.9-2.9 (m, 4 H), 2.52 (s, 3H), 2.9-3.45 (m, 2H), 5.4-5.65 (m, 1 H), 8-8.4 [a] (m, 1 H)
17b	*t*-Bu	92 (ether)	1695, 1730 (C=O), 1590 (C=N), 3290 (N-H)	1.34 (s, 9 H), 1.9-2.9 (m, 4 H), 2.51 (s, 3 H), 5.3-5.75 (m, 1 H), 8-8.35 [a] (m, 1 H)
17c	Ph	150 (methanol/ether)	1490, 1550 (C=C arom), 1590 (C=N), 1690, 1730 (C=O), 3160 (N-H)	1.8-3.2 (m, 4 H), 2.51 (s, 3 H), 5.45-5.9 (m, 1 H), 6.75-7.6 (m, 5 H), 9.9-10.7 [a] (m, 1 H)
17d	*p*-Cl-Ph	176 (toluene)	1490, 1545 (C=C arom), 1590 (C=N), 1690, 1715 (C=O), 3120 (N-H)	2-2.9 (m, 4 H), 2.52 (s, 3 H), 5.45-5.8 (m, 1 H), 8.05-8.5 (m, 4 H), 10.1-10.4 [a] (m, 1 H)
17e	*m,p*-Cl_2-Ph	176 (toluene)	1475, 1530 (C=C arom), 1590 (C=N), 1690, 1710 (C=O), 3200 (N-H)	2-3.15 (m, 4 H), 2.54 (s, 3 H), 5.4-5.75 (m, 1 H), 7-7.4 (m, 2 H), 7.6-7.8 (m, 1 H), 10.1-10.3 [a] (m, 1 H)
17f	*m*-CF_3-Ph	114 (toluene)	1490, 1550 (C=C arom), 1595 (C=N), 1685, 1715 (C=O), 3220 (N-H)	2.1-3.25 (m, 4 H), 2.54 (s, 3 H), 5.5-5.8 (m, 1 H), 7.1-7.9 (m, 4 H), 10.05-10.25 [a] (m, 1 H)
18c	Ph	190 (methanol)	1730, 1760 (C=O), 3220 (N-H)	2.2-2.6 (m, 4 H), 2.51 (s, 3 H), 4.2-4.65 (m, 1 H), 6.8-7.6 (m, 5 H), 10-10.35 [a] (m, 1 H)
18d	*p*-Cl-Ph	186 (methanol)	1720, 1740 (C=O), 3200 (N-H)	2.1-2.9 (m, 4 H), 2.55 (s, 3 H), 4.1-4.5 (m, 1 H), 7.1-7.55 (m, 4 H), 9.95-10.4 [a] (m, 1 H)
18e	*m,p*-Cl_2-Ph	180 (CH_2Cl_2)	1730 (C=O), 3150 (N-H)	2.3-2.8 (m, 4 H), 2.60 (s, 3 H), 4.1-4.5 (m, 1 H), 7.25-7.75 (m, 3 H), 10-10.3 [a] (m, 1 H)
19e	*m,p*-Cl_2-Ph	147 (methanol)	1575 (C=N), 1675, 1720 (C=O), 3070, 3180, 3340 (N-H)	2.14 (s, 3 H), 2.2-2.65 (m, 4 H), 3.77 (s, 3 H), 4.3-4.7 (m 1 H), 7.15-7.7 (m, 3 H), 7.95-8.1 [a] (m, 1 H), 8.75-8.95 [a] (m, 1 H)
21	Me	135 (methanol)	1720 (C=O), 3280 (N-H)	(200 MHz) 2.2-2.6 (m, 4 H), 3.17 (s, 1.5 H), 3.20 (s, 1.5 H), 3.26 (s, 3H), 3.68 (s, 3 H), 8.02 [a] (bs, 1 H), 8.82 [a] (bs, 1 H)
22	Ph	130 (ether)	1720, 1700 (C=O), 3240 (N-H)	(200 MHz) 2.5-2.7 (m, 4 H), 3.72 (s, 3 H), 7.3-7.6 (m, 8 H), 7.77 (d, J = 7.6 Hz, 2 H), 8.26 [a] (bs, 1 H), 10.43 [a] (bs, 1 H)

[a] This peak disappears upon addition of deuterium oxide.

Scheme 5

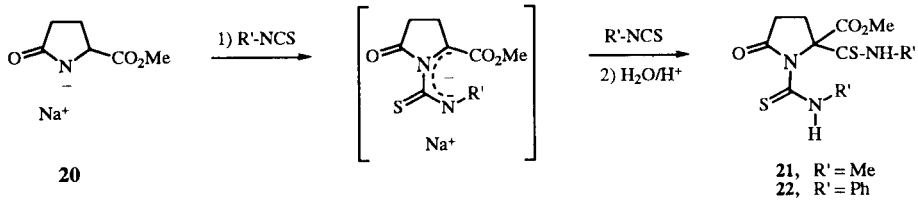


18 **19**

presence of catalysts no reaction was observed. It is known that the reaction of sodium caprolactam with phenyl isothiocyanate yields a monoaddition product [10]. Under these conditions, the sodium salt of methyl pyroglutamate **20** [11] reacts with methyl and phenyl isothiocyanate to give adducts **21** and **22**.

The new *N*-carbamoylpyroglutamic derivatives were tested *in vitro* against a variety of fungi and in general they have weak biological properties. These compounds

Scheme 6



20 **21**, R' = Me; **22**, R' = Ph

Table 2

Yield and Analyses of New Compounds

No.	Yield % [a]	Formula	Calcd./Found					
			C	H	N	O	Cl	F
16a	88	$C_{11}H_{18}N_2O_4$	54.53	7.49	11.56	26.42		
			54.79	7.61	11.39	26.10		
16b	97	$C_{11}H_{18}N_2O_4$	54.53	7.49	11.56	26.42		
			54.44	7.40	11.46	26.66		
16c	82	$C_{13}H_{14}N_2O_4$	59.54	5.38	10.68	24.40		
			59.58	5.17	10.84	24.57		
16d	85	$C_{13}H_{13}N_2O_4Cl$	52.62	4.42	9.44	21.57	11.95	
			52.29	4.38	9.43	21.75	12.35	
16e	86	$C_{13}H_{12}N_2O_4Cl_2$	47.15	3.65	8.46		21.41	
			47.05	3.69	8.52		21.63	
16f	71	$C_{14}H_{13}N_2O_4F_3$	50.92	3.97	8.48			17.26
			50.91	3.94	8.45			17.07
17a	78	$C_{12}H_{18}N_4O_3$	54.12	6.81	21.04	18.02		
			54.46	6.79	21.09	18.25		
17b	74	$C_{12}H_{18}N_4O_3$	54.12	6.81	21.04			
			54.04	6.56	21.33			
17c	80	$C_{14}H_{14}N_4O_3$	58.74	4.93	19.57	16.77		
			58.81	4.88	19.46	17.02		
17d	96	$C_{14}H_{13}N_4O_3Cl$	52.43	4.09	17.47	14.96	11.05	
			52.59	3.93	17.66	15.21	11.41	
17e	93	$C_{14}H_{12}N_4O_3Cl_2$	47.34	3.41	15.77		19.96	
			47.43	3.48	15.76		19.92	
17f	78	$C_{15}H_{13}N_4O_3F_3$	50.85	3.70	15.81			16.09
			51.20	3.67	15.63			15.96
18c	63	$C_{14}H_{14}N_4O_3$	58.74	4.93	19.57			
			58.38	4.80	19.29			
18d	57	$C_{14}H_{13}N_4O_3Cl$	52.43	4.09	17.47		11.05	
			52.25	3.82	17.64		11.31	
18e	50	$C_{14}H_{12}N_4O_3Cl_2$	47.34	3.41	15.77	13.51		
			47.45	3.35	15.62	13.12		
19e	85 [b]	$C_{15}H_{16}N_4O_4Cl_2$	46.53	4.16	14.47	16.53		
			46.13	4.01	14.48	16.74		
21	20	$C_{10}H_{15}N_3O_3S_2$	41.51	5.22	14.52			
			41.57	5.19	14.79			
22	16	$C_{20}H_{19}N_3O_3S_2$	58.09	4.63	10.16			
			58.28	4.68	10.13			

[a] Crude yield. [b] Yield from **18e**.

were also screened for antitumor activity [12], but none had interesting properties.

The physical properties of the new compounds are reported in Tables 1 and 2.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 700 spectrometer and the nmr spectra on a Hitachi Perkin Elmer R-600 at 60 MHz, using tetramethylsilane as an internal reference. Elemental analyses were performed by the Service Central de Microanalyses of CNRS in Vernaison, France. Melting points, ir spectra and elemental analyses were not determined for moisture sensitive compounds. Pyroglutamic acid was a gift of UCIB, Ivry-la-Bataille, France, which can provide this acid in bulk quantities.

N-(4-Chlorophenylcarbamoyl)-2-pyrrolidone (**7d**).

N-Trimethylsilylpyrrolidinone (**3**) [13] (0.9 g, 0.006 mole) was added (syringe) to 4-chlorophenyl isocyanate (1.8 g, 0.012 mole) and the mixture was stirred at room temperature for 1 hour. Methanol (5 ml) was added and the mixture was stirred at room temperature for 4 hours. The solid (1.3 g) was filtered then recrystallized, giving a 93% yield of compound **7d** identical with the known compound [2,7].

N-Phenylcarbamoyl-2-pyrrolidone (**7c**).

This compound was obtained following the same method as for **7d**, in 36% yield, identical to the known compound [2,7].

N,N-Dimethylamino-Δ_1-pyrroline (**8**).

Dimethylcarbamyl chloride (28 ml, 0.305 mole) in tetrahydrofuran (10 ml) was slowly added (30 minutes) to a solution of *N*-trimethylsilylpyrrolidinone (**3**) [13] in tetrahydrofuran (10 ml), and the mixture was refluxed for 24 hours. The residue obtained after evaporation was distilled. The first distillation fraction, bp

45-65 (0.15 mm Hg) was a mixture of 2-pyrrolidinone and of pyrroline **8** whose the structure was proved by comparison with the product obtained following literature methods [14].

Methyl *N*-(Tertiobutylcarbamoyl)pyroglutamate (**16b**).

t-Butyl isocyanate (26.0 ml, 0.228 mole) in toluene (50 ml) was slowly added (30 minutes) to a refluxing solution of methyl pyroglutamate (**10**) [15] (16.0 g, 0.112 mole) in toluene (50 ml), and the mixture was refluxed for 3 hours. Methanol (100 ml) was added and the solvents were evaporated giving 26.1 g of ester **16b** which was recrystallized.

Compounds **16** and **18** were obtained following the same procedure; for compounds **17**, the reflux time was 1 hour.

Methyl *N*-(Phenylcarbamoyl)pyroglutamate (**16c**).

From Methyl Pyroglutamate (**10**).

Compound **16c** was obtained in 82% yield following the same procedure as for **16b**.

From Methyl *N*-Trimethylsilylpyroglutamate (**13**).

Triflic acid (1 drop, 0.3 mmole) was added to a mixture of methyl *N*-trimethylsilylpyroglutamate (**13**) [6b] (2.0 g, 9 mmoles) and phenyl isocyanate (2.1 g, 19 mmoles), and the solution was stirred at room temperature for 17 hours. Methanol (10 ml) was added. After a few hours, the solid was filtered, giving a 59% yield of compound **16c.**

2-(3,4-Dichlorophenylcarbamoyl)-4-methyl-1,6-dioxo-6,7,8,8a-tetrahydro-1*H*-pyrrolo[1,2d][l,2,4-triazine] (**18e**).

Methyl *N*-(l-Carbamoylhydrazonoethyl)pyroglutamate (**19e**).

A solution of 3,4-dichlorophenyl isocyanate (4.5 ml, 0.024 mole) in toluene (5 ml) was slowly added (30 minutes) to a refluxing mixture of triazinone **12** [5] in toluene (25 ml). After refluxing for 3 hours, methanol (2 ml) was added. The solid obtained (2.15 g, 50% yield) was compound **18e**. This product was dissolved in refluxing methanol, giving **l9e** (85% from **18e**) which can be recyclized in an nmr tube by addition of deuterated sodium hydroxide.

Methyl 1,2-Bismethylthiocarbamoylpyroglutamate (**21**).

A solution of methyl pyroglutamate (15.0 g, 0.105 mole) in toluene (25 ml) was slowly added (30 minutes) to a suspension of sodium hydride (2.6 g, 0.108 mole) in toluene (50 ml), and the mixture was stirred at room temperature for 1 hour. Methyl isothiocyanate (15.4 g, 0.210 mole) in toluene (20 ml) was added and the mixture was stirred at room temperature for 12 hours. Water (100 ml) was added, and the organic phase was washed with dilute hydrochloric acid giving a precipitate. After filtration, the solution was dried and then evaporated giving a solid. The combined solids (6.1 g) were recrystallized in methanol, giving pure compound **21**.

Compound **22** was obtained following the same procedure by using benzene as a solvent, refluxing for 45 minutes and purification by chromatography (silica gel, ether).

REFERENCES AND NOTES

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