HETEROCYCLES, Vol. 11, 1978

THE REACTION OF AMIDES WITH DIETHYLTHIOCARBAMOYL CHLORIDE: A NEW PROCEDURE FOR THE PREPARATION OF NITRILES AND THIOAMIDES[1]

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Primary amides reacted with diethylthiocarbamoyl chloride to give their nitriles, and also tertiary amides gave their thioamides smoothly. In the presence of amines, the above reactions yielded the amidines, quinazolines or ureas, according to a variety of amides and amines used.

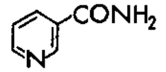
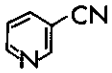
Although dialkylthiocarbamoyl chloride provided an excellent method for the synthesis of thiophenols[2] or phenylisothiocyanates,[3] little attention has been paid to their potential use in the amide field. We now wish to report the first results in a study of the reactions of amides with diethylthiocarbamoyl chloride.

Nitriles

Primary amides and thioamides reacted with diethylthiocarbamoyl chloride to give their nitriles, and also ureas can be converted to their cyanamides as is seen in the Table I. The following procedure represents a typical example for the formation of nitrile.

A mixture of 1.0 g of benzamide and 1.25 g (equimolar amount) of diethylthiocarbamoyl chloride in 10 mL of dichloroethane was stirred at 80° for 1 hr. The resulting diethylamine hydrochloride (783 mg) was filtered off and the organic layer was washed with water, dried over sodium sulfate and evaporated.

Table I. Synthesis of Nitriles

Entry	Substrate	Product[a]	Yield (%)
1	$C_6H_5CONH_2$	C_6H_5CN	78.4
2	$C_6H_5CSNH_2$	C_6H_5CN	88.5
3	$C_6H_5CH_2CONH_2$	$C_6H_5CH_2CN$	75.1
4			35.8
5	$C_6H_5NHCONH_2$	C_6H_5NHCN[b]	34.2
6	$(CH_3)_2N\text{-}CONH_2$	$(CH_3)_2NCN$	32.1

All the reactions were carried out at the equimolar ratio for the substrate and diethylthiocarbamoyl chloride.

[a] Isolated diethylamine hydrochloride: 86.7% for Entry 1, 87.1% for Entry 2, 92.8% for Entry 3, 87.1% for Entry 4.

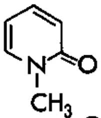
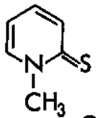
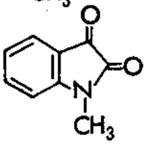
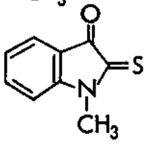
[b] Equimolar ratio of aluminium chloride for diethylthiocarbamoyl chloride was used.

The residue was distilled to afford benzonitrile, 667 mg, bp_{39} 96-98° (Entry 1).

Thioamides

The reaction of tertiary amides with diethylthiocarbamoyl chloride yielded their thioamides and diethylcarbamoyl chloride. A variety of examples of the thiation of tertiary amides are listed in the Table II. A typical one is as follows.

Table II. Synthesis of Thioamides

Entry	Substrate	Product[a]	Yield (%)
7	$C_6H_5N(CH_3)COC_6H_5$	$C_6H_5N(CH_3)CSC_6H_5$	76.7
8	$C_6H_5N(CH_3)CHO$	$C_6H_5N(CH_3)CHS$	70.5
9			25.2
10			42.0
11	$(CH_3)_2NCHO$	$(CH_3)_2NCHS$	46.9

[a] Diethylcarbamoyl chloride was isolated in 65.7% yield together with thioamide for Entry 7. No attempt to isolate diethylcarbamoyl chloride from the reaction mixture was made for Entries 8-11.

Entry 8: Diethylthiocarbamoyl chloride (1.1 molar equivalent), aluminium chloride (0.1 molar equivalent).

Entry 9: Diethylthiocarbamoyl chloride (1.1 molar equivalent), aluminium chloride (0.2 molar equivalent).

Entry 10: Diethylthiocarbamoyl chloride (1.5 molar equivalent), aluminium chloride (0.2 molar equivalent).

Entry 11: Diethylthiocarbamoyl chloride (1.3 molar equivalent).

A mixture of 2.0 g of N-methylbenzanilide and 1.57 g (1.1 molar equivalent) of diethylthiocarbamoyl chloride and 126 mg (0.1 molar equivalent) of anhydrous aluminium chloride in 20 mL of dichloroethane was stirred at 80° for 1 hr. The reaction mixture was distilled to remove diethylcarbamoyl chloride, 924 mg, bp$_{15}$ 77°. The residue was neutralized with sodium bicarbonate and extracted with dichloromethane. The dichloromethane was distilled and the residue was chromatographed on silica gel to give 1.65 g of N-methylthiobenzanilide, mp 100-101.5° (Entry 7).

The process is simple and convenient, but, it is obvious that there are certain limitations to the application of the method. For instance, upon reaction with diethylthiocarbamoyl chloride, secondary amides did not give any clear products.

The amides derived from aliphatic amines reacted with diethylthiocarbamoyl chloride to give their thioamides, in the absence of catalyst while the thiation of the amides derived from aromatic amines took place only when anhydrous aluminium chloride was used as a catalyst. These facts are consistent with the reaction of phenylurea requiring anhydrous aluminium chloride for the cyanamide formation. The contrast between these two can be explained in terms of the basicities of the amides.

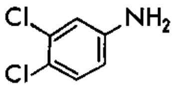
Amidines, Quinazolines and Ureas[4]

(Amidines) The reaction of N,N-dimethylformamide with diethylthiocarbamoyl chloride in the presence of 3,4-dichloroaniline (**1**) gave the amidine (**2**) in 30.6% yield together with the thiourea (**3**) in 2.6% yield. An analogous reaction also took place with a variety of amides to give the amidines (**4**, **5**, **7**).

Table III. Synthesis of Amidines

Entry	Amine	Amide	Products
12	**1**	$(Me)_2NCHO$	**2** (30.6%), **3** (2.6%)
13	**1**	$(Me)_2NCOMe$	**4** (26.5%)
14	**1**	PhNHCOMe	**5** (10.4%)
15	**6**	$(Me)_2NCHO$	**7** (67.2%)

All the reactions were carried out at the molar ratio 1 : 1.3 : 1.3 for the amine, amide, and diethylthiocarbamoyl chloride (except Entry 15).
Entry 15: The molar ratio above was 1 : 33 : 3.



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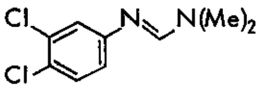

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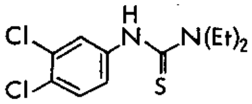

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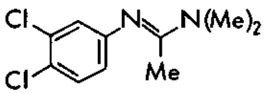

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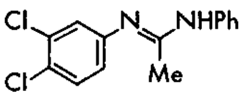

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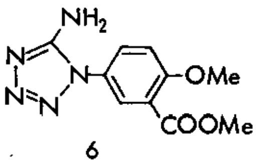

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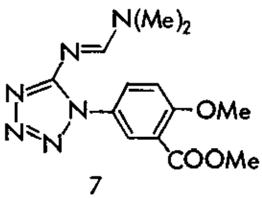

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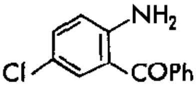
(Quinazolines) Although primary amide reacted with diethylthiocarbamoyl chloride to give the nitrile as described in the nitrile formation, formamide yielded the quinazolines (9, 12, 14) through amidine intermediates from O-aminobenzophenone (8), O-aminobenzonitrile (11) and methyl anthranilate (13) in the presence of diethylthiocarbamoyl chloride.

Table IV. Synthesis of Quinazolines

Entry	Amine	Amide	Products
16	8	$HCONH_2$	9 (67.7%), 10 (5.1%)
17	11	$HCONH_2$	12 (9.1%)
18	13	$HCONH_2$	14 (43.4%)

All the reactions were carried out at the molar ratio 1 :1 .3 :1 .3 for the amine, amide, and diethylthiocarbamoyl chloride.



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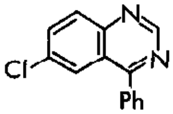

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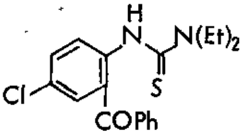

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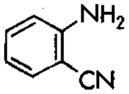

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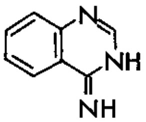

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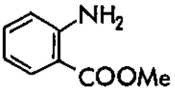

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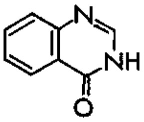


14

(Ureas) When benzylamine (15) was used instead of the above aromatic amines in the amidine formation, dibenzylurea (16) was isolated. Namely, the reaction of 15 with diethylthiocarbamoyl chloride and N,N-dimethylformamide gave 16 (6.8%) and 17 (4.8%). Under similar conditions, the reaction of 15 with diethylthiocarbamoyl chloride and N-methylformamide also gave 16 (11.1%) and 17 (10.4%). However, upon reaction with N,N-dimethylacetamide, which has no N-formyl group, 15 yielded 16 in poor yield (1.3%).

These results seem to suggest that the ketene intermediate reacted with excess benzylamine to yield the dibenzylurea.

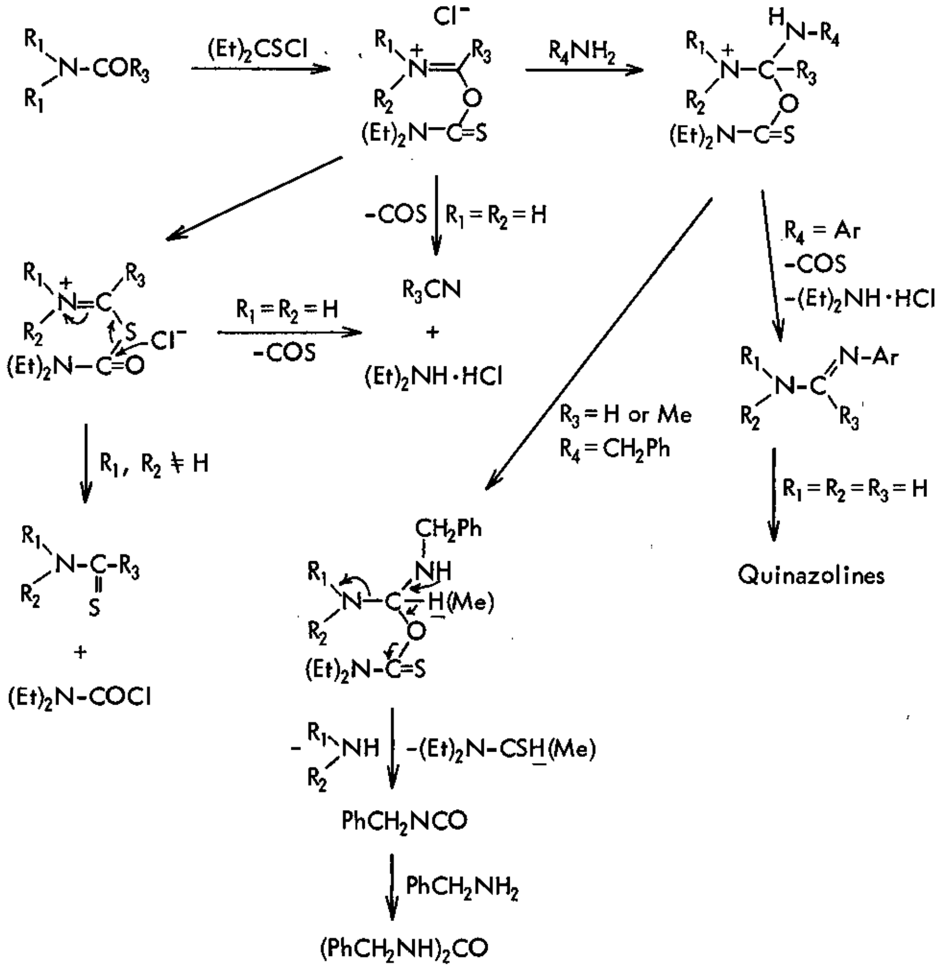
Table V. Synthesis of N,N'-dibenzylurea

Entry	Amine	Amide	Products
19	15	$(Me)_2NCHO$	16 (6.8%), 17 (4.8%)
20	15	$MeNHCHO$	16 (11.1%), 17 (10.4%)
21	15	$(Me)_2NCOMe$	16 (1.3%), 17 (8.9%)

All the reactions were carried out at the molar ratio 1 : 1.3 : 1.3 for the amine, amide, and diethylthiocarbamoyl chloride.

$PhCH_2NH_2$	$(PhCH_2NH)_2CO$	$PhCH_2NHCSN(Et)_2$
15	16	17

In summary, the reaction scheme of amides and diethylthiocarbamoyl chloride can reasonably be depicted as shown in the following figure.


R1 N-COR3 R1
(Et)2CSCl
Cl⁻
R1 + N=C R3 R2 O (Et)2N-C=S
R4NH2
H N-R4 R1 + N-C-R3 R2 O (Et)2N-C=S
-COS
R1 = R2 = H
R3CN
+
(Et)2NH·HCl
R1 + N=C R3 R2 S Cl⁻ (Et)2N-C=O
R1 = R2 = H
-COS
R4 = Ar
-COS
-(Et)2NH·HCl
R1 N-C N-Ar R2 R3
R3 = H or Me
R4 = CH2Ph
R1, R2 ≠ H
R1 = R2 = R3 = H
Quinazolines
R1 N-C-R3 R2 S
+
(Et)2N-COCl
CH2Ph NH R1 N-C H(Me) R2 O (Et)2N-C=S
- R1 NH R2
-(Et)2N-CSH(Me)
PhCH2NCO
PhCH2NH2
(PhCH2NH)2CO

References

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4 The structures of all the new compounds were supported by elemental analyses and their spectral (ir, nmr) properties.

Received, 21st August, 1978