21. A Novel Amination Reaction with Diphenyl Phosphorazidate: Synthesis of α-Amino-Acid Derivatives

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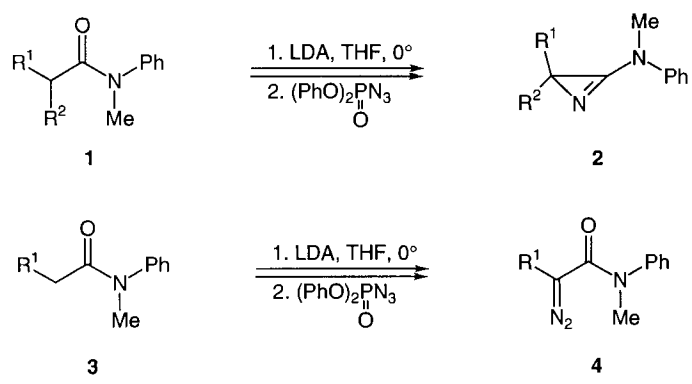
The reaction of enolates of α-unsubstituted carboxamides **3** with diphenyl phosphorazidate (DPPA) and di(*tert*-butyl) dicarbonate ('Boc anhydride') in THF at −78° yielded 2-{[(*tert*-butoxy)carbonyl]amino}carboxamides **5** (*Scheme 2*) which are derivatives of α-amino acids. In this reaction, DPPA acts as an electrophilic amination reagent. A reaction mechanism is proposed in *Scheme 3*.

1. Introduction. – Diphenyl phosphorazidate (DPPA) is well known as an azido-transfer reagent (*cf.* [1–3] and refs. cit. therein) and is, *e.g.*, often used to prepare acyl azides as activated acid derivatives in peptide syntheses. Recently, we have shown that the azido group of DPPA also substitutes the O-atom of enolates of *N*-methyl-*N*-phenylcarboxamides **1**, leading to azidoenamines which, by elimination of N_2, cyclize to give 3-amino-2*H*-azirines **2** [4] (*Scheme 1*). A different reaction occurred with enolates of α-unsubstituted carboxamides of type **3** and DPPA: α-diazocarboxamides **4** were formed as the sole product [4] (*Scheme 1*). In this case, DPPA acts as a diazo-transfer reagent.

In the present paper, a third reaction type of DPPA is described, in which it formally reacts as an amination reagent.

Scheme 1



1 **2** **3** **4**

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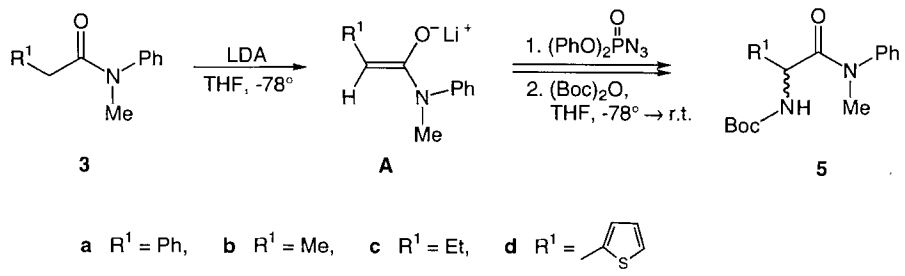
2. Results. – Solutions of enolates of α-unsubstituted *N*-methyl-*N*-phenylcarboxamides **3** in THF, prepared with lithium diisopropylamide (LDA) at −78°, were treated with DPPA (1.1 equiv.; 5 min at −78°) and then with di(*tert*-butyl) dicarbonate ('Boc-anhydride', $(Boc)_2O$); 2 equiv.; 6 h, −78° to room temperature). After chromatography (SiO_2), the amino-acid derivatives **5** were isolated as colorless or slightly yellow solids in 70–80% yield (*Scheme 2*). The structures of **5a–d** were elucidated by means of their spectroscopic data. In the case of **5d**, the structure was confirmed by an X-ray crystal-structure determination (*Fig. 1*).

Scheme 2



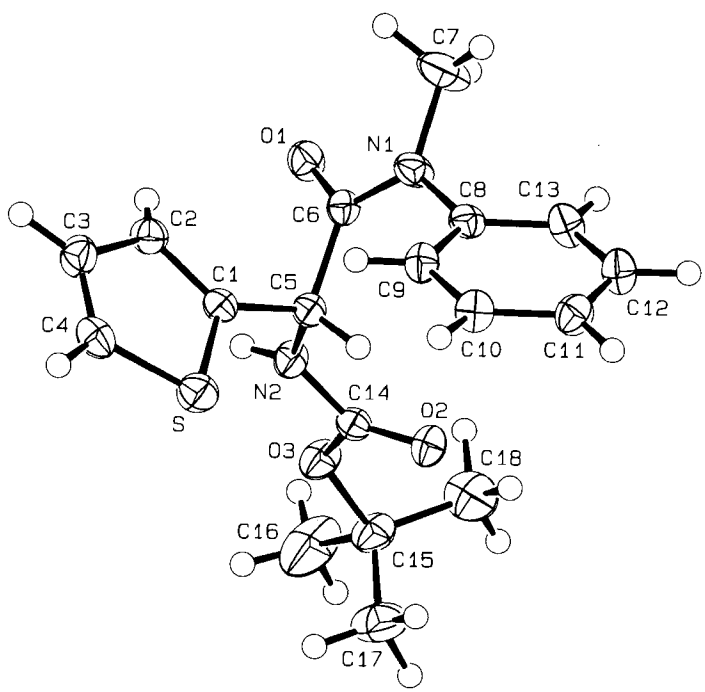
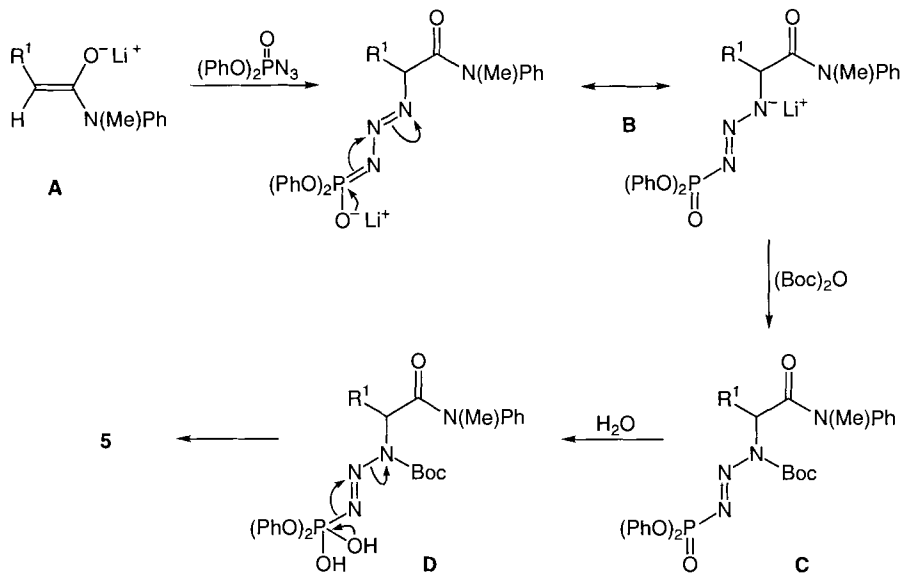


Fig. 1. *ORTEP Plot* [5] *with 50% probability ellipsoids of the crystal structure of* **5d**

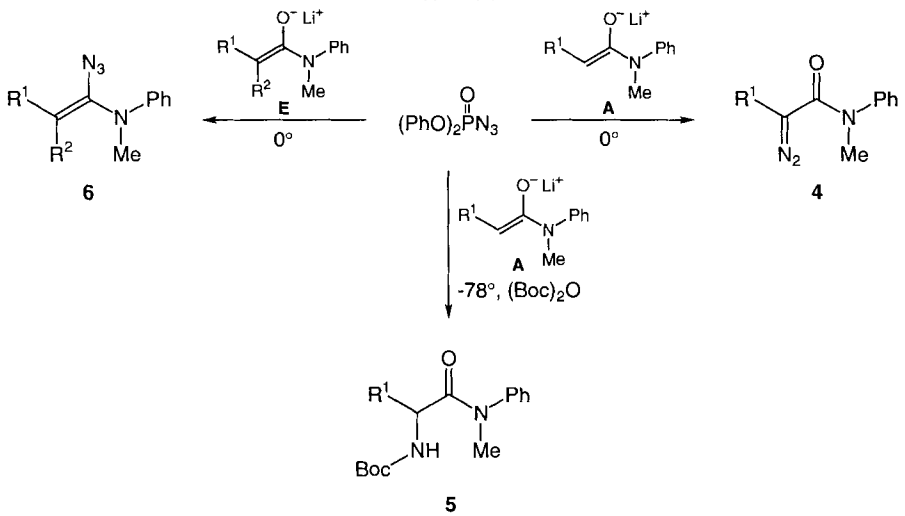
Scheme 3



A likely reaction mechanism for the formation of **5** is proposed in *Scheme 3*. The enolate **A** reacts as a C-nucleophile with the terminal N-atom of DPPA to give **B** (*cf.* also [4]), which, as a triazenyl anion, is trapped by the electrophilic $(Boc)_2O$ to give **C**. During workup, **C** decomposes, probably *via* fragmentation of **D**, leading to **5**.

3. Discussion. – We showed that DPPA with lithium enolates of carboxamides can react either as an N_3-, an N_2-, or an 'NH_2'-transfer reagent (*Scheme 4*). With 2,2-disubsti-

Scheme 4



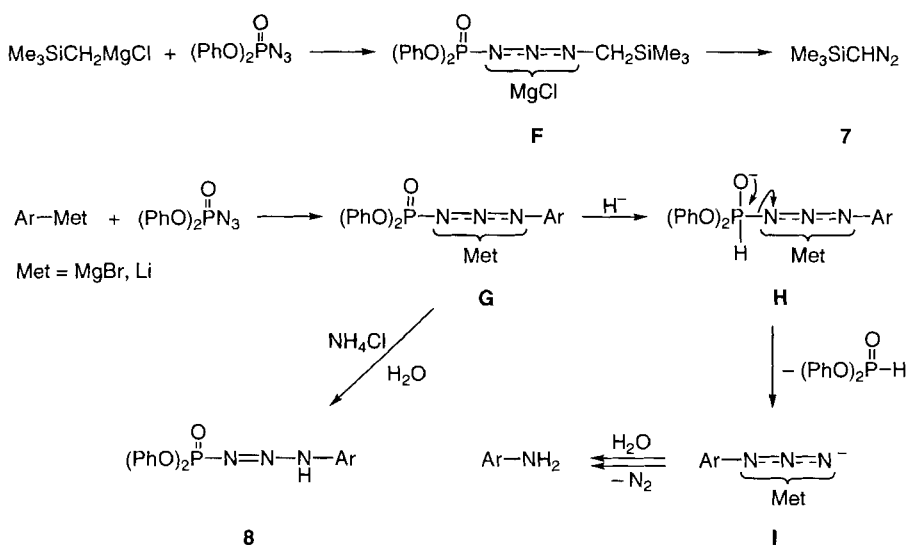
tuted enolates **E** at 0°, azidoenamines **6**, the precursors of 3-amino-2*H*-azirines **2**, are formed. The kind of product formed in the reaction of DPPA with 2-monosubstituted enolates **A** depends on the reaction conditions. Whereas at 0°, α-diazoamides **4** are formed, *N*-protected α-amino-acid derivatives **5** are obtained at −78° after trapping with $(Boc)_2O$.

Precedents are known for all three reaction types. As mentioned in the introduction (see also [4]), the most common reaction of DPPA is the N_3 transfer with carboxylic acids to give acyl azides, which are used as activated acid derivatives in peptide syntheses and for preparing carboxamides, esters, and thioesters [1] [3a] [6] [7]. In boiling alcohols, the acyl azides undergo a *Curtius* rearrangement to give urethanes [3b], and after hydrolysis and decarboxylation, the corresponding amines are obtained [3] [8]. An N_3 transfer also occurs with alcohols in the presence of Ph_3P and diethyl azodicarboxylate (modified *Mitsunobu* reaction) [2], and in 1,3-dipolar cycloadditions [8].

In comparison with the N_3 transfer reactions, only a few examples of diazo transfer with DPPA are known. *E.g.*, diazo(trimethylsilyl)methane (**7**) is formed in good yield in the reaction of DPPA with the *Grignard* reagent from (chloromethyl)trimethylsilane [9] (*Scheme 5*)[3]). The intermediate of the reaction is a triazene derivative of type **F**[4])[5]).

The potential of DPPA as an 'NH_2'-transfer reagent (electrophilic amination reagent) was also shown by *Shioiri* and coworkers [12] [13]. Aromatic and heteroaromatic *Grignard* and lithium compounds in Et_2O at low temperature reacted with DPPA to give triazene derivatives **G**, which were reduced *in situ* with $LiAlH_4$ or $NaAl_2(OCH_2CH_2OMe)_2$

Scheme 5



[3]) In a sluggish reaction, alkyl ethenyl ethers and dibutyl phosphorazidate gave low yields of diazomethane [10].

[4]) The position of the double bond in the triazene derivatives was not established.

[5]) The formation of 1,3-disubstituted triazenes in the reaction of organic azides and *Grignard* or lithium compounds is well known [11].

to give the aromatic amines. When the reaction mixture was treated with an aqueous NH_4Cl solution instead of the hydride reagent, intermediate **G** was trapped as the triazene **8** which was isolated in good yield. Reduction of **8** with hydrides or decomposition under alkaline or acidic conditions again yielded the aromatic amine. The proposed mechanism for the hydride reduction [12] is shown in *Scheme 5*, and the hydrolytic decomposition may proceed in an analogous way to that depicted in *Scheme 3*.

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Experimental Part

General. See [14]. Unless otherwise stated, IR spectra in $CHCl_3$, ^1H- (300 MHz) and ^{13}C-NMR (50,4 MHz) in $CDCl_3$. CI-MS: with 2-methylpropane or NH_3 as carrier gas.

General Procedure. To a soln. of 3 mmol of carboxamide **3** in 6 ml of dry THF, 1.1 equiv. of LDA (1.5M in cyclohexane) were added at −78° under Ar. After stirring the mixture for 1 h, 1.1 equiv. of DPPA were added slowly. The mixture was stirred at −78° for 5 min, and then a soln. of 2 equiv. of $(Boc)_2O$ in 3 ml of dry THF was added at once. The mixture was further stirred for 6 h, raising the temp. from −78° to r.t. After evaporation the residue was purified by chromatography (SiO_2, hexane/AcOEt).

2-{[(tert-Butoxy)carbonyl]amino}-N-methyl-2,N-diphenylacetamide (Boc-Phe-N(Me)Ph; **5a**): 815 mg (80%). Colorless solid. M.p. 102–103°. IR: 3430*m*, 1705*s*, 1655*s*, 1595*m*, 1490*s*, 1455*m*, 1425*w*, 1390*s*, 1370*m*, 1315*w*, 1300*w*, 1250*m*, 1165*s*, 1120*m*, 1075*w*, 1060*m*, 1025*w*, 1015*w*, 1000*w*, 965*w*, 950*w*, 890*w*, 875*w*, 840*w*, 820*w*, 700*s*, 660*w*. ^1H-NMR: 7.4–7.1 (*m*, 7 arom. H); 6.95–6.9 (*m*, 3 arom. H); 5.84 (*d*, $J = 8$, NH); 5.25 (*d*, $J = 8$, H–C(2)); 3.26 (*s*, MeN); 1.39 (*s*, Me_3C). ^{13}C-NMR: 170.2, 154.6 (2*s*, 2 C=O); 142.0, 137.7 (2*s*, 2 arom. C); 129.4, 128.2, 128.0, 127.8, 127.7, 127.5 (6*d*, 10 arom. CH); 79.3 (*s*, Me_3C); 55.5 (*d*, C(2)); 37.8 (*q*, MeN); 28.2 (*q*, Me_3C). CI-MS: 341 (100, $[M + 1]^+$).

2-{[(tert-Butoxy)carbonyl]amino}-N-methyl-N-phenylpropanamide (**5b**): 617 mg (74%). Colorless powder. M.p. 96–98°. IR: 3425*m*, 1705*s*, 1645*s*, 1590*m*, 1500*s*, 1490*s*, 1450*m* 1420*m*, 1390*m*, 1365*m*, 1330*w*, 1300*w*, 1245*m*, 1165*s*, 1120*m*, 1090*m*, 1060*m*, 1025*m*, 1000*w*, 915*w*, 890*w*, 855*m*, 695*s*, 660*w*. ^1H-NMR: 7.45–7.35 (*m*, 3 arom. H); 7.3–7.2 (*m*, 2 arom. H); 5.29 (*d*, $J = 7.5$, NH); 4.35–4.3 (*m*, H–C(2)); 3.27 (*s*, MeN); 1.41 (*s*, Me_3C); 1.10 (*d*, $J = 7$, Me). ^{13}C-NMR: 172.9, 154.6 (2*s*, 2 C=O); 142.5 (*s*, 1 arom. C); 129.7, 127.9, 127.2 (3*d*, 5 arom. CH); 78.9 (*s*, Me_3C); 46.6 (*d*, C(2)); 37.5 (*q*, MeN); 28.1 (*q*, Me_3C); 18.7 (*q*, Me). CI-MS: 279 (100, $[M + 1]^+$).

2-{[(tert-Butoxy)carbonyl]amino}-N-methyl-N-phenylbutanamide (**5c**): 665 mg (76%). Colorless crystals. M.p. 98–100°. IR: 3425*m*, 1705*s*, 1645*s*, 1590*m*, 1500*s*, 1490*s*, 1460*m*, 1420*m*, 1390*m*, 1365*m*, 1330*w*, 1295*m*, 1275*m*, 1245*m*, 1160*s*, 1120*m*, 1070*m*, 1050*m*, 1020*m*, 1005*w*, 985*w*, 960*m*, 900*w*, 855*w*, 825*w*, 695*s*, 660*w*. ^1H-NMR: 7.45–7.3 (*m*, 3 arom. H); 7.25–7.15 (*m*, 2 arom. H); 5.22 (*d*, $J = 7.5$, NH); 4.3–4.25 (*m*, H–C(2)); 3.28 (*s*, MeN); 1.65–1.5 (*m*, $MeCH_2$); 1.42 (*s*, Me_3C); 0.73 (*t*, $J = 7.5$, $MeCH_2$). ^{13}C-NMR: 172.2, 154.5 (2*s*, 2 C=O); 142.6 (s, 1 arom. C); 129.6, 127.8, 127.2 (3*d*, 5 arom. CH); 78.9 (*s*, Me_3C); 51.7 (*d*, C(2)); 37.4 (*q*, MeN); 28.1 (*q*, Me_3C); 26.1 (*t*, $MeCH_2$); 9.4 (*q*, $MeCH_2$). CI-MS: 293 (100, $[M + 1]^+$).

α-{[(tert-Butoxy)carbonyl]amino}-N-methyl-N-phenylthiophene-2-acetamide (**5a**): 725 mg (70%). Yellowish crystals. M.p. 104–106°. IR: 3420*m*, 1705*s*, 1655*s*, 1590*m*, 1490*s*, 1450*m*, 1420*m*, 1390*m*, 1365*m*, 1315*w*, 1295*w*, 1260*m*, 1245*m*, 1160*s*, 1120*m*, 1070*w*, 1060*m*, 1020*m*, 1010*w*, 990*w*, 940*w*, 870*w*, 850*w*, 835*w*, 695*s*, 660*w*. ^1H-NMR: 7.45–7.4 (*m*, 3 arom. H); 7.35–7.25 (*d*-artig, 1 arom. H); 7.2–7.0 (*m*, 2 arom. H); 6.85–6.8 (*t*-artig, 1 arom. H); 6.7–6.65 (*d*-artig, 1 arom. H); 5.74 (*d*, $J = 8$, NH); 5.53 (*d*, $J = 8$, H–C(2)); 3.30 (*s*, MeN); 1.40 (*s*, Me_3C). ^{13}C-NMR: 169.7, 154.5 (2*s*, 2 C=O); 142.1, 140.3 (2*s*, 2 arom. C); 129.6, 128.2, 127.5, 126.4, 125.6 (5*d*, 8 arom. CH); 79.7 (*s*, Me_3C); 50.6 (*d*, C(2)); 37.9 (*q*, MeN); 28.3 (*q*, Me_3C). CI-MS: 347 (100, $[M + 1]^+$).

Crystal Structure Determination of **5d** (see *Table* and *Figs. 1* and *2*)[6]. The intensities were collected on a *Rigaku-AFC5R* diffractometer in the ω-2θ-scan mode using graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å) and a 12-kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects and an absorption correction was applied using DIFABS [15]. Data collection and refinement parameters

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[6]) Atomic coordinates, bond lengths, and bond angles were deposited with the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, England.

Table. *Crystallographic Data for Compound* **5d**

	5d		**5d**
Crystallized from	MeOH	Space group	$P\bar{1}$
Empirical formula	$C_{18}H_{22}N_2O_3S$	Z	2
Formula weight	346.44	D_{calc} [g cm^{-3}]	1.249
Crystal color, habit	colorless, prism	Absorption coefficient μ(MoK_α) [mm^{-1}]	0.1840
Crystal temp. [K]	173 (1)		
Crystal dimensions [mm]	0.30 × 0.33 × 0.40	Absorption correction min, max	0.794, 1.120
Crystal system	triclinic	2θ (max) [°]	60
Lattice parameters		Total reflections measured	5629
Reflections for unit cell determination	25	Symmetry-independent reflections	5360
2θ range [°]	$39 < 2\theta < 40$	Reflections observed ($I > 3\sigma(I)$)	4084
a [Å]	10.607 (4)	Variables	306
b [Å]	10.976 (4)	Final R	0.0420
c [Å]	8.218 (2)	R_w[a])	0.0445
α [°]	100.86 (2)	Weights	$1/w = \sigma^2(F_o) + (0.005F_o)^2$
β [°]	95.58 (2)	Goodness of fit s	2.445
γ [°]	98.74 (3)	Final Δ_{max}/σ	0.0004
V [Å^3]	920.9 (5)	$\Delta\rho$ (max, min) [e Å^{-3}]	0.28, −0.33

[a]) Function minimized $\Sigma w(|F_o| - |F_c|)^2$.

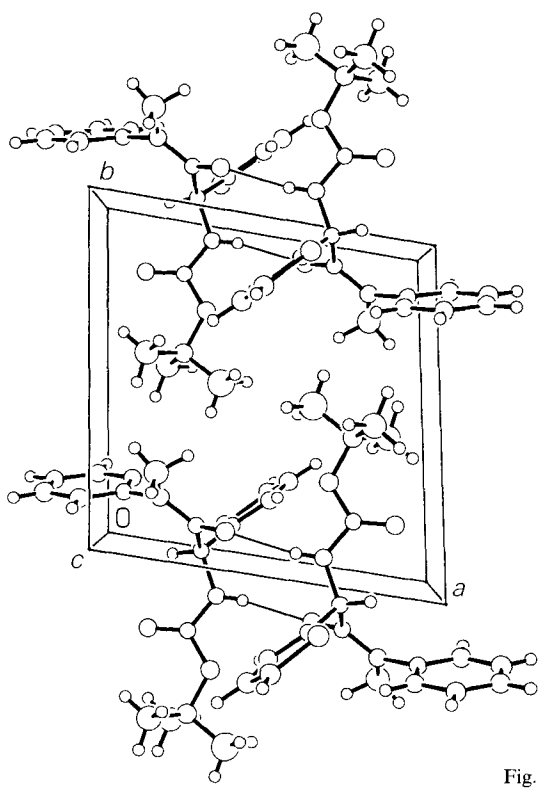

Fig. 2. *Crystal packing of* **5d**

are listed in the *Table*, views of the molecule and crystal packing are shown in *Figs. 1* and *2*. The structure was solved by direct methods using SHELXS86 [16], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were located in a difference electron density map and were refined isotropically. All refinements were carried out on F using full-matrix least-squares procedures. A correction for secondary extinction was applied (coefficent $6.56 \cdot 10^{-7}$). Neutral atom scattering factors for non-H-atoms were taken from [17a] and the scattering factors for H-atoms from [18]. Anomalous dispersion effects were included in F_{calc} [19]; the values for f' and f'' were those of [17b]. All calculations were performed using the TEXSAN crystallographic software package [20].

The NH group of each molecule acts as a donor for an intermolecular H-bond. The corresponding acceptor atom is the amide O-atom of a neighboring molecule, which is related to the first one by a centre of inversion. The H-bonding, therefore, links the molecules into dimers (*Fig. 2*).

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