Photolytic Synthesis of *N*-(2-Ethylbutyryl)-*N'*-substituted Imidodicarbonic Diamides

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The isocyanate type intermediate, photochemically generated from 5,5-diethyl-hexahydropyrimidine-2,4,6-trione, reacts smoothly with various amino nucleophiles yielding *N*-(2-ethyl-butyryl)-*N'*-substituted imidodicarbonic diamides. The advantages and limitations of the method are discussed.

The *N*-acyl-*N'*-substituted imidodicarbonic diamides show various biological activities, e.g. sedative and hypnotic[1] or antiinflammatory and antipyretic properties.[2] Several methods for the preparation of these compounds are described in the

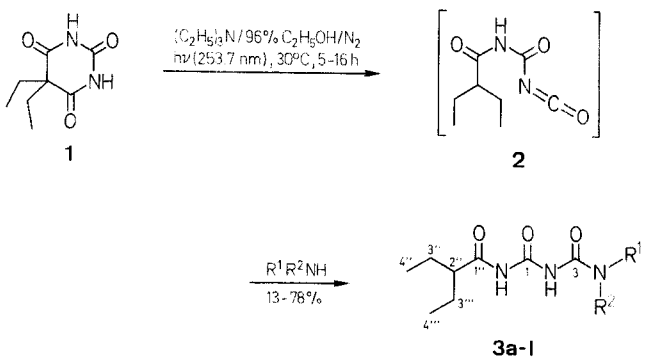
Table 1. *N*-(2-Ethylbutyryl)-*N'*-substituted Imidodicarbonic Diamides **3**.

Product 3	R^1	R^2	Irradiation Time (h)	Yield[a] (%)	m.p.[b] (°C)	Molecular Formula[c] or Lit. m.p. (°C)	IR[d] ν (cm^{-1})
a	CH_3	H	6	52	162–164	$C_9H_{17}N_3O_3$ (215.3)	3335, 3228, 3169 (NH); 1747, 1690 (C=O)
b	*n*-C_4H_9	H	10	76	96–97	$C_{12}H_{23}N_3O_3$ (257.3)	3336, 3228, 3174 (NH); 1726, 1702, 1682 (C=O).
c	*c*-C_6H_{11}	H	10	66	142–144	$C_{14}H_{25}N_3O_3$ (283.4)	3325, 3224, 3175 (NH); 1727, 1678 (C=O)
d	$C_6H_5CH_2$	H	10	78	139–141	$C_{15}H_{21}N_3O_3$ (291.3)	3337, 3236, 3177 (NH); 1736, 1681 (C=O)
e	$C_6H_5CH(CH_3)$	H	10	76	91–93	$C_{16}H_{23}N_3O_3$ (305.4)	3324, 3230, 3166 (NH); 1734, 1700, 1682 (C=O)
f	C_6H_5	H	16	23	124–126	$C_{14}H_{19}N_3O_3$ (277.3)	3361, 3234, 3148 (NH); 1737, 1698 (C=O)
g	4-$CH_3C_6H_4$	H	16	25	138–140	$C_{15}H_{21}N_3O_3$ (291.3)	3234, 3152 (NH); 1732, 1710, 1694 (C=O)
h	C_2H_5	C_2H_5	10	60	108–109	104[4]	3196, 3150 (NH); 1774, 1676, 1650 (C=O)
i	$-(CH_2)_5-$		10	70	114–115.5	114–115[4]	3200, 3143 (NH); 1778, 1686, 1668 (C=O)
j	C_6H_5NH	H	10	30	172–173	$C_{14}H_{20}N_4O_3$ (292.3)	3348, 3272, 3100 (NH); 1714, 1684 (C=O)
k	$HOOC(CH_2)_3$	H	10	47	128–130	$C_{12}H_{21}N_3O_5$ (287.3)	3360, 3327, 3226, 3168 (NH, OH); 1723, 1701, 1678 (C=O)
l	$HOOCCH(CH_3)$	H	5	13	174–175	$C_{11}H_{19}N_3O_5$ (273.3)	3302, 3236, 3154, 3110 (NH, OH); 1724, 1701, 1678 (C=O)

[a] Yield of isolated product.
[b] Uncorrected m.p.'s measured on a Boethius apparatus.
[c] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.22, N ± 0.28.
[d] IR spectra taken on Specord 75 IR (Zeiss, Jena), in suspension (nujol).

literature, such as the acylation of the imidodicarbonic diamide,[1-3] the reaction between acyl isocyanates and urea,[4] or the condensation of the allophanyl chloride with acid amides.[1] These methods allow the synthesis mainly of *N*-acylimidodicarbonic diamides of various yields.

However, the preparation of the *N*-acyl-*N'*-substituted derivatives is restricted by the very limited availability of the appropriate substrates. In a previous paper, we showed that the photolysis of 5,5-diethylhexahydropyrimidine-2,4,6-trione (**1**) in ethanol solution, in the presence of ammonia, dimethylamine or piperidine, yields the appropriate *N*-(2-ethylbutyryl)-*N'*-substituted imidodicarbonic diamides **3** *via* an intermediate of the isocyanate type **2** and subsequent attack of the nucleophilic reagent.[5] As a continuation of that study, we have now adopted this method to the preparative scale.

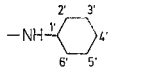
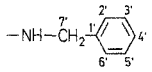
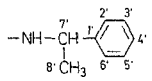
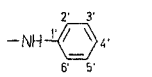
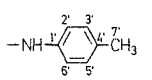
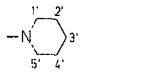
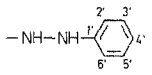


We selected several primary and secondary amines containing aliphatic, alicyclic or aromatic substituents, as well as phenylhydrazine and two amino acids, as the nucleophilic reagents for the trapping reaction (Table 1). The reaction was carried out in ethanol solution under nitrogen in the presence of triethylamine as a base, which is necessary to produce the monoionized form of **1**.[5] The intermediate **2** was generated by irradiation with monochromatic UV light (253.7 nm). The structure of the appropriate *N*-(2-ethylbutyryl)-*N'*-substituted imidodicarbonic diamides **3** was confirmed by microanalysis, IR (Table 1) and ^{13}C-NMR spectra (Table 2).

The resonance signals of the 1''-CO carbon atom are found in a very narrow range ($\Delta\delta \leq 1.1$ ppm). The urea-type 1-CO and 3-CO resonances are within their typical range.[6] The differences between the 1-CO and 3-CO chemical shifts for particular derivatives are small ($0 \leq \Delta\delta \leq 1.8$ ppm) and only for those containing an *N'*-phenyl substituent are the positions of these signals more differentiated ($\Delta\delta = 2.5$ and 2.3 ppm for **3f** and **3g**, respectively).

Derivatives **3a–3e, 3h** and **3i** were obtained in reasonable yield (52–78%), while **3f, 3g** and **3j–3l** in rather moderate yield (13–47%). The significantly higher yields of **3h** (60%) and **3i** (70%) compared to those given in the literature[4] proves the advantages of the presented method for their preparation. Lower yields for the reactions with aromatic amines (**3f, 3g**) or phenylhydrazine (**3j**) can be attributed to their lower nucleophilicity in relation to other amines investigated. The preparation of the sodium salt in water/ethanol solution is required for the reaction with alanine because of a very low solubility of both alanine and its triethylamine salt in ethanol. Therefore, the relatively small yield in this case (**3l**) may be explained by the competitive OH^- attack. The reaction profits from the high quantum yield ($\varnothing = 0.20$) for the photocleavage of **1** as compared to other 5,5-disubstituted derivatives ($\varnothing$ 0.02–0.08).[7] Thus, modification of the acyl group in **3** will probably be difficult with our synthetic procedure.

Table 2. ^{13}C-NMR Data for *N*-(2-Ethylbutyryl)-N'-substituted Imidodicarbonic Diamides **3**.[a]

Product 3	Chemical Shifts δ (ppm)								
	Carbonyl groups			$-NR^1R^2$ substituents					
	1''	1 and 3	Structure	1'	2' or 2' = 6'	3' or 3' = 5'	4'	7'	8'
[b]	179.3	153.4; 152.2	$-NH_2$						
a	179.2	153.0; 152.0	$-NH-CH_3$	26.4					
b	178.9	152.0; 152.0	$-NH-CH_2-CH_2-CH_2-CH_3$	38.8	31.3	19.4	13.5		
c	179.1	152.3; 151.4		48.3	32.5	25.3	24.4		
d	179.1	152.5; 152.0		139.2	128.6	127.5	127.3	43.1	
e	179.1	152.3; 151.5		143.9	128.8	127.3	126.0	49.2	22.6
f	179.1	152.2; 149.7		137.5	119.9	129.0	123.9		
g	179.3	152.2; 149.9		135.0	120.1	133.4	129.7	20.6	
h	179.0	151.3; 149.5	$-N(CH_2CH_3)_2$	41.5	13.7				
i	178.3	151.2; 149.5		44.9	25.3	23.7			
j	179.6	153.6; 151.8		149.2	112.8	129.5	119.9		
k	179.1	152.4; 151.9	$-NH-CH_2-CH_2-CH_2-COOH$	38.8	31.2	24.9	174.4		
l	179.4	152.2; 151.9	$-NH-CH-CH_3-COOH$	48.6	18.6	173.9			

[a] Tesla BS 567 A 25 MHz, in DMSO-d_6.
For **3a–31:** $\delta_{2''} = 49.2 - 49.6$ ppm; $\delta_{3''} = \delta_{3'''} = 24.5 - 24.8$ ppm; $\delta_{4''} = \delta_{4'''} = 11.4 - 11.7$ ppm.
[b] Chemical shifts for N-(2-ethylbutyryl)imidodicarbonic diamide, obtained previously.[5]

N-(2-Ethylbutyryl)N'-substituted Imidodicarbonic Diamides 3a–k; General Procedure:
5,5-Diethylhexahydropyrimidine-2,4,6-trione (**1**; 2.25 g, 12.5 mmol), triethylamine (5.05 g; 50 mmol; or 6.3 g, 62.5 mmol, for reaction with γ-aminobutyric acid and methylamine hydrochloride) the appropriate nucleophilic reagent (12.5 mmol) are dissolved in 96% ethanol (230 ml). The reaction mixture is placed in the photoreactor tube (height 58 cm, diameter 5.5 cm, thickness of irradiated layer 2.5 mm) equipped with cooling jacket and immersion low pressure mercury lamp TUV 30W (Philips) protected by a quartz tube. The reaction mixture is thermostated at 30 °C, degassed with nitrogen for 1 h, and irradiated for 6–16 h. The reaction mixture is then concentrated under reduced pressure at 30 °C to a volume of 15 ml, diluted with water (15 ml), acidified with normal hydrochloric acid to pH 4, heated gently to the dissolution of precipitate or oily layer and kept overnight in the refrigerator. The colorless crystals are filtered and recystallized, if necessary, from ethanol/water.

N-(2-Ethylbutyryl)-N'-(1-carboxyethyl)imidodicarbonic Diamide (3l):
DL-Alanine (2.3 g, 25 mmol) is dissolved in 1 normal sodium hydroxide (25 ml). The solution is diluted with hot 96% ethanol (200 ml). After cooling to 30 °C, **1** (2.25 g, 12.5 mmol) is dissolved in the reaction mixture, which is then irradiated as above for 5 h. The reaction mixture is acidified with 1 normal hydrochloric acid (25 ml), evaporated under reduced pressure to a volumne of 50 ml, basified with 1 normal sodium hydroxide to pH 8, diluted with phosphate buffer (pH = 8; 50 ml) and extracted with ethyl acetate (3 × 50 ml). The water layer is acidified with 1 normal hydrochloric acid to pH 1 and evaporated to a volume of 20 ml. Then water is decanted and the oily residue is crystallized twice from ethanol-water mixture yielding colorless crystals of **31**.

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