2-Cyano-2-isocyanoalkanoates in Multicomponent Reactions

by **Stefan Müller** and **Richard Neidlein***

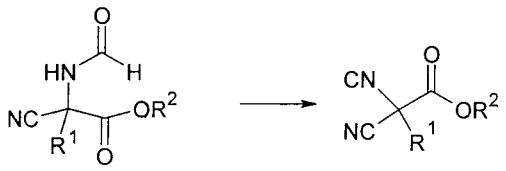
Pharmazeutisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 364, D-69120 Heidelberg

Dedicated to Professor Dr. Dr. *h. c. mult. Siegfried Hünig* on the occasion of his 80th birthday

The reactivity of 2-cyano-2-isocyanoalkanoates **2** in multi-component reactions was investigated, *i.e.*, in the *Passerini* reaction and the *Ugi*-four-component condensation (see *Schemes 2* and *3*, resp.). Interestingly, the structure of the 2-cyano-2-isocyanoalkanoates **2** strictly limited the possible starting materials. Only the combination of aliphatic aldehydes, halogenated acetic acid derivatives, and nonaromatic amines gave satisfactory results, *i.e.*, provided depsidipeptides **5** (*Tables 3* and *4*) and depsitripeptides **9** (*Tables 6*), respectively. Some of the products of the multicomponent reactions were transformed into crystalline compounds by decarboxylation (see *Scheme 4*). After fractional crystallization, the molecular structure of one of the decarboxylated depsitripeptides, *i.e.*, of **10**, was established by X-ray crystallography.

Introduction. – In previous publications, our group reported the synthesis of 2-cyano-2-isocyanoalkanoates **2** [1] (*Scheme 1*), their application to the preparation of 5,5-disubstituted 2,4-dithiohydantions [2], and their use as versatile synthons for the assembly of imidazoles [3].

Scheme 1. *Synthesis of 2-Cyano-2-isocyanoalkanoates* **2**. See *Table 1* for R^1 and R^2.



1a–l **2a–l**

To further explore the reactivity of compounds of type **2**, we decided to investigate the role of **2** as key compound in multicomponent reactions, for example the *Passerini* reaction [4] or the *Ugi*-four-component condensation (*Ugi-4CC*) [5].

Results and Discussions. – Different new 2-cyano-2-isocyanoalkanoates **2** were synthesized according to [1] with the aim to study their behavior in multicomponent reactions (*Table 1*). Thus, the multicomponent *Passerini* reaction was investigated and optimized with a mixture of *tert*-butyl α-cyano-α-isocyano-4-methylbenzenepropanoate (**2a**), chloroacetic acid (**3**), and 2-methylpropanal (**4**) under different conditions leading to **5** (*Scheme 2*). As the solvent, CH_2Cl_2 was used, and the ratio of **3**/**4**/**2a** was

Scheme 2. *Model Reaction for the* Passerini *Reaction with 2-Cyano-2-isocyanoalkanoates* **2**

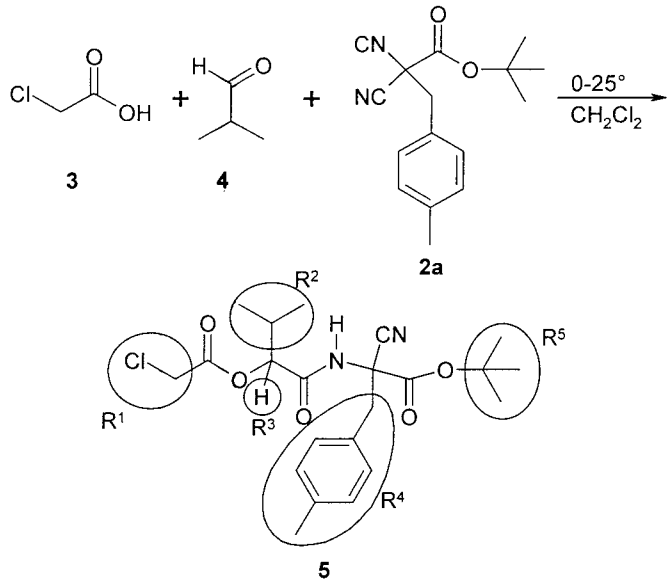


Table 1. *2-Cyano-2-isocyanoalkanoates* **2** *Used in the Multicomponent Reactions* (*cf. Scheme 1*)

	R^1	R^2
2a	4-Me–C_6H_4–CH_2	^{t}Bu
2b	4-Me–C_6H_4–CH_2	Et
2c	4-F–C_6H_4–CH_2	^{t}Bu
2d	4-F–C_6H_4–CH_2	Et
2e	4-MeO–C_6H_4–CH_2	^{t}Bu
2f	4-NO_2–C_6H_4–CH_2	Et
2g	4-NO_2–C_6H_4–CH_2	^{t}Bu
2h	4-Cl–C_6H_4–CH_2	Et
2i	4-Cl–C_6H_4-CH_2	^{t}Bu
2j	4-^{t}Bu–C_6H_4–CH_2	^{t}Bu
2k	C_6H_5–CH_2	^{t}Bu
2l	Et	^{t}Bu

chosen as 1.5 : 1.5 : 1, because, for other *Passerini* reactions, these conditions were shown to be optimal [6].

The model reaction was optimized at different temperatures (*Table 2*). Stirring the mixture for 2 h at 0° and then for 48 h at room temperature appeared to be the best compromise between the thermolability of the 2-cyano-2-isocyanoalkanoates **2** and the necessary activation of the components. The solvent is a critical parameter for good yields in multicomponent reactions. Because compounds **2** are stable for a longer time only in CH_2Cl_2, the use of other solvents was not possible. Therefore, mixtures of CH_2Cl_2 and other solvents had to be used. As shown in *Table 2*, CH_2Cl_2 or mixtures of CH_2Cl_2/MeOH, depending on the solubility of the starting materials, were optimal.

Table 2. *Optimization of Reaction Conditions of the* Passerini *Reaction of* **2a**, **3**, *and* **4** *Yielding* **5** (see *Scheme 2*); *Variation of the Temperature and Reaction Time* (CH_2Cl_2) *and Variation of the Solvent*

Temperature [°]	0	0	0	0	0	0, 25[a])	0, 25[a])	0, 25[a])	0, 25[b])	0, 25[b])	0, 25[b])
Time [h]	6	12	24	48	72	6, 12[a])	6, 24[a])	6, 48[a])	2, 24[b])	2, 48[b])	2, 72[b])
Yield [%]	10	11	17	25	27	22	32	51	56	68	68
Solvent	CH_2Cl_2	$CHCl_3$	MeOH	EtOH	^{i}PrOH	MeCN	AcOH	CH_2Cl_2/MeOH 1:1		CH_2Cl_2/MeOH 3:1	
Yield [%]	68	53	65	61	48	27	62	65		68	

[a]) 6 h at 0° and then 12, 24, or 48 h at 25°. [b]) 2 h at 0° and then 24, 48, or 72 h at 25°.

Finally, the influence of the acid and the carbonyl compound on the *Passerini* reaction with **2** was investigated. For this purpose, the reactions were carried out under the optimized conditions, changing the acid, **2**, and the carbonyl compound. The success of these reactions depended on all three components: ketones and aromatic aldehydes did not react at all (*Tables 3* and *4*). Good yields were obtained only with aliphatic aldehydes, which can be explained by steric hindrance. The influence of the acid component is possibly similar. Only acids exerting low steric hindrance, such as halogenated acetic acid derivatives, resulted in high yields. The dependency of the *Passerini* reaction on the substituent R^4 of **2** was relatively low compared to the other two components: compounds with $R^4 = ArCH_2$ gave slightly better yields than the ones with $R^4 = Et$. The *tert*-butyl esters produced higher yields and crystallized easier than the ethyl esters. In summary, the best results in the *Passerini* reaction were obtained with an aliphatic aldehyde, a halogenated acetic acid, and a 4-substituted *tert*-butyl α-cyano-α-isocyanobenzenepropanoate.

Table 3. *Depsidipeptides* **5** *Prepared from Ethyl 2-Cyano-2-isocyanoalkanoates* ($R^5 = C_2H_5$)

	R^1	R^2	R^3	R^4	Yield [%]
	CH_2Cl	Me	Me	4-Me–C_6H_4–CH_2	0
	CH_2Cl	Ph	Me	4-Me–C_6H_4–CH_2	0
	CH_2Cl	CCl_3	CCl_3	4-Me–C_6H_4–CH_2	0
	CH_2Cl	Ph	H	4-Me–C_6H_4–CH_2	0
	CH_2Cl	Ph	Me	4-Me–C_6H_4–CH_2	0
5a	CH_2Cl	Et	H	4-Me–C_6H_4–CH_2	27
5b	CH_2Cl	Me_2CH	H	4-Me–C_6H_4–CH_2	26
5c	CF_3	Me_2CH	H	4-Me–C_6H_4–CH_2	28
5d	4-NO_2–C_6H_4–CH_2	Me_2CH	H	4-Me–C_6H_4–CH_2	23
5e	$CHCl_2$	Me_2CH	H	4-F–C_6H_4–CH_2	27

All obtained depsidipeptides **5** crystallized as long pale needles. Because an additional chiral center was formed during the *Passerini* reaction with the asymmetric **2**, compounds **5** were mixtures of two diastereoisomers (NMR). The diastereomeric compounds could be separated by fractional crystallization from Et_2O followed by column chromatography (SiO_2/CH_2Cl_2). Unfortunately, the separated diastereoisomers did not yield crystals suitable for X-ray crystal-structure analysis, thus preventing the determination of their configurations by this means.

The second investigated reaction, the *Ugi*-four-component condensation (*Ugi-4CC*), was elaborated by *Ugi* in 1959 [7]. This reaction furnishes a tripeptid starting

Table 4. *Depsidipeptides* **5** *Prepared from* tert-*Butyl 2-Cyano-2-isocyanoalkanoates* ($R^5 = {}^t$Bu)

	R^1	R^2	R^3	R^4	Yield [%]
	CH_2Cl	Me	Me	4-Me−C_6H_4−CH_2	0
	CH_2Cl	$PhCH_2$	Me	4-Me−C_6H_4−CH_2	0
	CH_2Cl	CCl_3	CCl_3	4-Me−C_6H_4−CH_2	0
	CH_2Cl	Ph	H	4-Me−C_6H_4−CH_2	0
	CH_2Cl	Ph	Me	4-Me-C_6H_4−CH_2	0
5f	CH_2Cl	Me_2CH	H	4-Cl−C_6H_4−CH_2	61
5g	CH_2F	MeC*H*	H	4-Me−C_6H_4−CH_2	39
5h	CH_2Br	Me_2CH	H	Et	30
5i	CH_2Br	Me_2CH	H	4-Cl−C_6H_4−CH_2	51
5j	CH_2Br	Et	H	4-Me−C_6H_4−CH_2	49
5k	CH_2I	Me_2CH	H	4-Me−C_6H_4−CH_2	63
5l	CH_2I	Et	H	$PhCH_2$	46
5m	CH_2I	Me_2CH	H	$PhCH_2$	53
5n	CH_2I	Me_2CH	H	4-Cl−C_6H_4−CH_2	57
5o	CH_2I	Me_2CH	H	4-MeO−C_6H_4−CH_2	50
5p	CH_2I	Me	H	$PhCH_2$	36
5q	CH_2CN	Me_2CH	H	$PhCH_2$	27
5r	$CHCl_2$	Me_2CH	H	4-Me−C_6H_4−CH_2	58
5s	$CHCl_2$	Et	H	4-NO_2−C_6H_4−CH_2	55
5t	$CHCl_2$	Me_2CH	H	4-NO_2−C_6H_4−CH_2	58
5u	$CHCl_2$	Me_2CH	H	4-MeO−C_6H_4−CH_2	53
5v	$CHCl_2$	Me_2CH	H	4-F−C_6H_4−CH_2	60
5w	$CHCl_2$	$MeCH_2CH_2$	H	4-F−CH_4−CH_2	53
5x	$CHCl_2$	Me_2CH	H	Et	45
5y	CCl_3	Me_2CH	H	4-NO_2−C_6H_4−CH_2	38
5z	CF_3	Me_2CH	H	$PhCH_2$	33
5aa	CF_3	Me_2CH	H	4-Me−C_6H_4−CH_2	38
5ab	$Me_2C(OH)$	Me_2CH	H	4-F−C_6H_4−CH_2	7
5ac	4-F−C_6H_4−CH_2	Me_2CH	H	4-Me−C_6H_4−CH_2	22
5ad	4-F−C_6H_4−CH_2	Me_2CH	H	4-NO_2−C_6H_4−CH_2	28
5ae	4-F−C_6H_4−CH_2	Et	H	Et	17
5af	4-NO_2−C_6H_4−CH_2	Me_2CH	H	$PhCH_2$	35
5ag	4-NO_2−C_6H_4−CH_2	Me_2CH	H	4-Me−C_6H_4−CH_2	23
5ah	4-NO_2−C_6H_4−CH_2	Me_2CH	H	Et	11

with an amino component, a carbonyl compound, an acid, and an isocyanide. The success of the reaction depends on the starting materials used. Investigations with **2** similar to those described for the *Passerini* reaction allowed us to establish the conditions for a successful transformation to depsitripeptides in an *Ugi-4CC*. Thus, the temperature and the solvents were optimized with the mixture of *tert*-butyl 2-cyano-2-isocyanobutanoate (**2l**), propanamine (**6**), 2-methylpropanal (**7**), and iodoacetic acid (**8**) (*Scheme 3*). The ratio of **2l**:**6**:**7**:**8** was chosen as 1.5:1.5:1.5:1, as in most of the *Ugi-4CCs* [8]. First, the reactions were carried out under the conditions of the *Passerini* reaction, *i.e.*, stirring in CH_2Cl_2 for 2 h at 0° and then for 48 h at 25°, but no formation of depsitripeptide was observed. Only the corresponding *Passerini* products were isolated, the amino component did not take part in the reaction. Variation of the temperature was also not successful, but, on changing the solvent to different alcohols, the desired depsitripeptide **9a** was obtained, MeOH being the best solvent (*Table 5*).

Scheme 3. *Model Reaction for the* Ugi-4CC *Reaction with 2-Cyano-2-isocyanoalkanoates* **2**

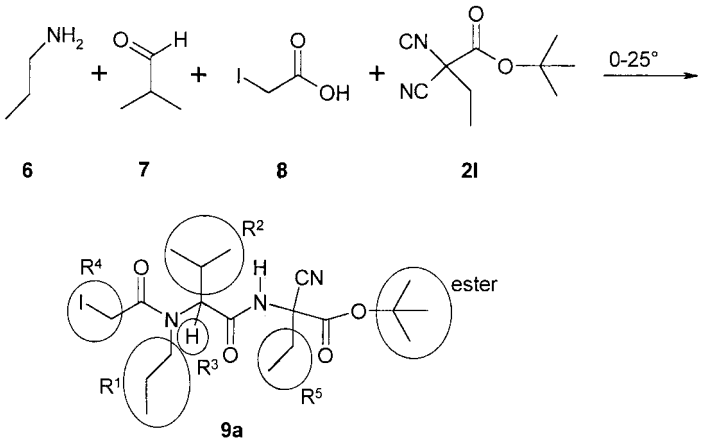


Table 5. *Solvent Dependence of the Model* Ugi-4CC *Reaction with* **21**: *Yields of* **9a** (see *Scheme 3*)

Solvent	EtOH	MeOH	PrOH	^{i}PrOH	BuOH	^{i}BuOH
Yield [%]	36	43	34	34	21	22

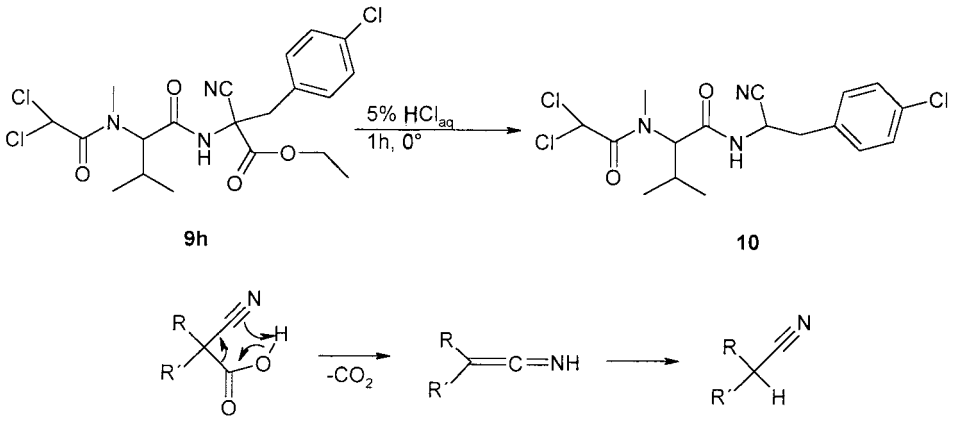
With **2** as starting material in the *Ugi-4CC*, the *Passerini* reaction competes successfully, depending on the solvent. With solvents other than alcohols, *e.g.*, also $CHCl_3$, MeCN, or AcOH, no product of an *Ugi-4CC* could be isolated. Such effects were described for other *Ugi-4CCs*, too [9]. For the model reaction carried out in MeOH, variation of temperature gave the same results as for the *Passerini* reaction. Again, this effect can be explained by the compromise between the thermolability of the 2-cyano-2-isocyanoalkanoates **2** and the necessary activation of the starting materials. The best results for the *Ugi-4CC* with **2** were obtained in MeOH as solvent by stirring at 0° for 2 h and then for 48 h at room temperature. Having optimized the reaction conditions, the influence of all four reaction components on the *Ugi-4CC* was investigated as in the case of the *Passerini* reaction. The results were similar: the influence of **2** was negligible, and only aliphatic aldehydes as carbonyl compounds, halogenated acetic acid derivatives, and aliphatic or benzylic primary amines gave satisfying yields (*Table 6*). This could be explained by steric hindrances of compounds differing from the above mentioned [10].

In analogy to the *Passerini* reaction, the formation of diastereoisomers was observed, which could be separated only by column chromatography (SiO_2, MeOH/CH_2Cl_2 2:1). An attempt to hydrolyze the pure diastereoisomers **9** failed since the expected free acids were not stable; they easily decarboxylated to give the corresponding substituted cyano derivatives as exemplified by **9a** → **10** (*Scheme 4*). These cyano derivatives could be separated by fractional crystallization from ^{i}PrOH as colorless platelets, and the molecular structure of **10** was established by X-ray crystallography (*Fig.*). The relative configuration of the two chiral centers could be determined as (R*,R*) as shown for *rel*-(2*R*)-*N*-[(1*R*)-2-(4-chlorophenyl)-1-cyanoethyl]-2-[(dichl oroacetyl)methylamino]-3-methylbutanamide (**10**) (*Fig.*).

Table 6. *Depsitripeptides* **9** *Synthesized by the* Ugi-4CC *with 2-Cyano-2-isocyanoalkanoates as Educt*

	R^1	R^2	R^3	R^4	R^5	Ester	Yield [%]
	$MeCH_2CH_2$	Me	Me	CH_2I	4-Me–C_6H_4–CH_2	^{t}Bu$_3$	0
	$MeCH_2CH_2$	Ph	Me	CH_2I	4-Me–C_6H_4–CH_2	^{t}Bu	0
	$MeCH_2CH_2$	Ph	H	CH_2I	4-Me–C_6H_4–CH_2	^{t}Bu	0
	$MeCH_2CH_2$	Me	Me	CH_2I	4-Cl–C_6H_4–CH_2	Et	0
	$MeCH_2CH_2$	Me_2CH	H	$PhCH_2$	4-Cl–C_6H_4–CH_2	^{t}Bu	0
	$PhCH_2$	Me_2CH	H	CH_2I	Et	^{t}Bu	0
9a	$MeCH_2CH_2$	Me_2CH	H	CH_2I	Et	^{t}Bu	27
9b	$MeCH_2CH_2$	Me_2CH	H	CH_2Br	4-NO_2–C_6H_4–CH_2	^{t}Bu	11
9c	$MeCH_2CH_2$	Me_2CH	H	$CHCl_2$	Et	^{t}Bu	56
9d	$MeCH_2CH_2$	Me_2CH	H	$CHCl_2$	4-F–C_6H_4–CH_2	^{t}Bu	29
9e	$MeCH_2CH_2$	Me_2CH	H	CH_2I	4-NO_2–C_6H_4–CH_2	Et	31
9f	Et	Me_2CH	H	$CHCl_2$	4-Me–C_6H_4–CH_2	^{t}Bu	25
9g	Me	Me_2CH	H	$CHCl_2$	4-Me–C_6H_4–CH_2	^{t}Bu	34
9h	Me	Me_2CH	H	$CHCl_2$	4-Cl–C_6H_4–CH_2	Et	15
9i	$PhCH_2$	Me_2CH	H	CH_2Cl	4-Me–C_6H_4–CH_2	^{t}Bu	43
9j	$PhCH_2$	Et	H	CH_2Cl	4-NO_2–C_6H_4–CH_2	^{t}Bu	29
9k	$PhCH_2$	Me_2CH	H	$CHCl_2$	4-Cl–C_6H_4–CH_2	^{t}Bu	46

Scheme 4. *Decarboxylation of Depsitripeptide* **9h**



Conclusions. – The use of 2-cyano-2-isocyanoalkanoates **2** in the *Passerini* reaction and the *Ugi-4CC* was explored. These reactions are limited to aliphatic aldehydes, halogenated acetic acid derivatives, and, in the *Ugi-4CC*, to primary nonaromatic amines. The products of the *Ugi-4CC* were transformed to the free acids, which decarboxylated immediately. After fractional crystallization, it was possible to establish the molecular structure of one of the decarboxylated compounds; further work in this direction is in progress.

We thank *BASF AG*, *Bayer AG*, and *Aventis AG*, the *Fonds der Chemischen Industrie*, as well as the *Deutsche Forschungsgemeinschaft* for support of this work. We are indebted to Dr. *W. Kramer* and Mrs. *Ute Hertle* for NMR spectra, to Mr. *H. Rudy* for mass spectra, and to Mr. *P. Weyrich* for elemental analyses. Special thanks go to Mr. *C. Krieger* for the X-ray analysis.

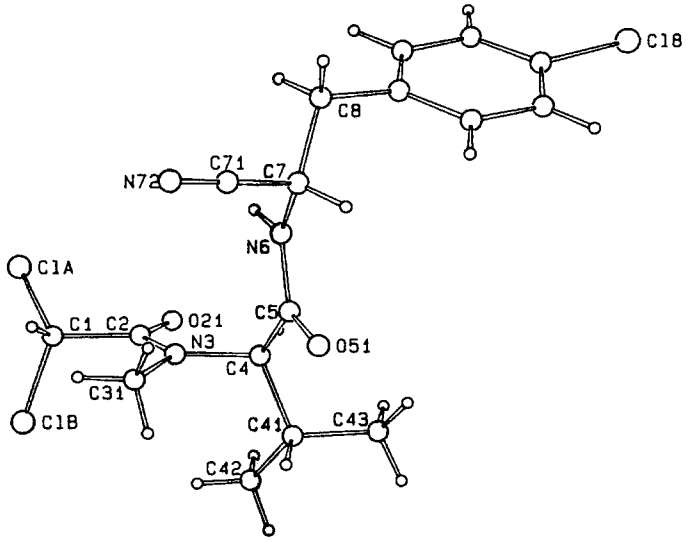


Figure. *Molecular structure of* **10**

Experimental Part

1. *General*. All reactions were carried out under Ar in flame-dried glassware. CH_2Cl_2 was freshly distilled from CaH; MeOH was freshly distilled from Mg; Et_2O was distilled from Na/benzophenone before use. Column chromatography (CC): silica gel (60–200 mesh) from *Merck KGaA*. M.p.: *Reichert* melting-point microscope; uncorrected. IR Spectra: KBr pellets; *Perkin-Elmer PE-1600-FT-IR* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: at 250.13 MHz with *Bruker WM-250* spectrometer, at 360.12 MHz with *Bruker AM-360* spectrometer; δ in ppm rel. to $SiMe_4$, J in Hz. ^{13}C-NMR Spectra: at 62.89 and 90.56 MHz with the same spectrometers. MS: *Varian MAT-311-A* spectrometer at 70 eV; *m/z* (rel. %). Elemental analyses: *Foss-Heraeus Vario EL*.

2. *Alkyl 2-Cyano-2-isocyanoalkanoates* (**2a**–**l**). Prepared according to [1]. All previously unknown 2-cyano-2-isocyanoalkanoates gave the characteristic physical data.

3. *Depsidipeptides* **5a**–**ah**. 3.1. *General Procedure*. To a soln. of **2** in CH_2Cl_2, the aldehyde and the acid (alkanoate/aldehyde/acid 1.1.5:1.5) are added under stirring at 0°. Solid components are dissolved in CH_2Cl_2 or in CH_2Cl_2/MeOH 3:1. After 20 min, the cooling bath is removed and the soln. stirred for 2 days. After evaporation the residue is dissolved in CH_2Cl_2 (10 ml), the soln. washed with sat. $NaHCO_3$ soln. (2 × 25 ml) and H_2O (20 ml), dried (Na_2SO_4 sicc.), and evaporated, and the remaining oil fractionated by crystallization from Et_2O. Then, the crystals were dissolved in CH_2Cl_2 and purified by CC (silica gel, CH_2Cl_2). Evaporation followed by crystallization yield pure depsidipeptides as pairs of diastereoisomers.

3.2. *Exemplary Data for Depsidipeptides*. 3.2.1. *Ethyl α-({2-[(Chloroacetyl)oxy]-3-methyl-1-oxobutyl}amino)-α-cyano-4-methylbenzenepropanoate* (**5b**). From ethyl α-cyano-α-isocyano-(4-methylbenzenepropanoate (**2b**; 894 mg, 3.7 mmol), 2-methylpropanal (**4;** 400 mg, 5.6 mmol, 0.51 ml), and chloroacetic acid (**3**; 528 mg, 5.6 mmol) in CH_2Cl_2/MeOH (30 ml). Crystallization gives 383 mg (26%) of a mixture of diastereoisomers (*cf.* ^{13}C-NMR). M.p. 128°. IR (KBr): 3399*s*, 2972*s*, 2249*m*, 1755*s*, 1794*s*, 1683*s*, 1515*s*, 1471*m*, 1399*m*, 1257*s*, 1050*s*, 1015*s*, 926*m*, 794*s*, 598*m*. ^{1}H-NMR ($CDCl_3$): 0.91 (*m*, *Me*$_2$CH), 1.26 (*t*, *Me*CH_2O); 2.34 (*s*, *Me*C_6H_4); 2.58 (*m*, Me_2CH); 3.32 (*d*, ^2J = 15.1, 1 H, $C_6H_4CH_2$); 3.55 (*d*, ^2J = 15.0, 1 H, $C_6H_4CH_2$); 3.99 (*d*, ^2J = 10.1, 1 H, ClH_2CO); 4.16 (*d*, ^2J = 10.9, 1 H, $ClCH_2CO$); 4.28 (*m*, $MeCH_2O$); 5.13 and 5.20 (2*d*, ^3J = 3.5 and 4.2, Me_2CHCH); 6.82 and 6.84 (2*s*, NH); 7.08–7.28 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 13.80, 13.85 (*Me*CH_2O); 16.70, 16.81 (1 Me of Me_2CH); 18.33, 18.36 (1 Me of Me_2CH); 21.11, 21.13 (*Me*C_6H_4); 30.91, 31.01 (Me_2CH); 40.37, 40.52 ($ClCH_2CO$); 41.12, 41.41 ($C_6H_4CH_2$); 56.89, 57.26 (C(α)); 63.96, 64.19 ($COOCH_2Me$); 78.77, 78.88 (Me_2CHCH); 115.71, 115.87 (CN); 128.19, 128.23, 129.76, 129.79, 129.86, 129.92, 138.65, 138.69 (6 arom. C); 165.38, 165.48 (CO); 166.06, 166.18 (CO); 168.32, 168.45 (CO). MS: 408 (2.4, $M^{+\cdot}$), 215 (36.92,

[M – NHCOCH(OCOCH$_2$Cl)CHMe$_2$]$^+$), 105 (100, MeC$_6$H$_4$CH2$^+$), 77 (10.23, [ClCH$_2$CO]$^+$), 55 (10.08, C$_4$H$_9^+$). Anal. calc. for C$_{20}$H$_{25}$ClN$_2$O$_5$: C 58.75, H 6.16, N 6.86; found: C 58.85, H 6.45, N 6.74.

3.2.2. tert-*Butyl α-Cyano-α-({2-[(dichloroacetyl)oxy]-3-methyl-1-oxobutyl}-amino)-4-methylbenzenepropanoate* (**5r**). From *tert*-butyl α-cyano-α-isocyano-4-methylbenzenepropanoate (**2a**; 750 mg, 2.8 mmol), 2-methylpropanal (**4**; 328 mg, 4.2 mmol, 0.2 ml), and dichloroacetic acid (542 mg, 4.2 mmol, 0.85 ml) in CH$_2$Cl$_2$/MeOH (20 ml). Crystallization followed by CC gives 439 mg (33%) of diastereoisomer I and 335 mg (25%) of diastereoisomer II of **5r**.

Diastereoisomer I: M.p. 138°. IR (KBr): 3294*s*, 2976*s*, 2733*s*, 2245*m*, 1753*s*, 1727*s*, 1676*s*, 1513*s*, 1280*s*, 1151*s*, 1014*s*, 939*m*, 814*s*, 756*s*, 674*m*. ^{1}H-NMR (CDCl$_3$): 1.01 (*d*, ^3J = 6.7, *Me*$_2$CH); 1.53 (*s*, ^{t}Bu); 2.32 (*s*, *Me*C$_6$H$_4$); 2.40 (*m*, Me$_2$C*H*); 3.29 (*d*, ^2J = 13.7, 1 H, C$_6$H$_4$C*H*$_2$); 3.65 (*d*, ^2J = 13.8, 1 H, C$_6$H$_4$C*H*$_2$); 5.25 (*d*, ^3J = 6.8, Me$_2$CHC*H*); 5.88 (*s*, Cl$_2$CH); 6.79 (*s*, NH); 7.05–7.27 (*m*, 4 arom. H). ^{13}C-NMR (CDCl$_3$): 16.54 (1 Me of Me$_2$CH); 18.32 (1 Me of Me$_2$CH); 21.05 (*Me*C$_6$H$_4$); 27.65 (*Me*$_3$); 31.18 (Me$_2$*C*H); 40.45 (C$_6$H$_4$*C*H$_2$); 57.03 (C(α)); 63.77 (Cl$_2$CH); 79.92 (Me$_2$CH*C*H); 86.32 (Me$_3$*C*); 115.87 (CN); 128.41, 129.57, 129.91, 138.35 (6 arom. C); 162.68 (CO); 163.85 (CO); 167.51 (CO). MS: 470 (0.57, M^+), 187 (42.04, MeC$_6$H$_4$CH$_2$C(CN)COO$^+$), 105 (100, MeC$_6$H$_4$CH$_2^+$), 57 (43.95, C$_4$H$_9^+$). Anal. calc. for C$_{22}$H$_{28}$Cl$_2$N$_2$O$_5$: C 56.06, H 5.99, N 5.94; found: C 55.97, H 6.13, N 5.92.

Diastereoisomer II: Purity 95%. M.p. 102°. ^{1}H-NMR (CDCl$_3$): 1.10 (*d*, ^3J = 6.8, *Me*$_2$CH); 1.60 (*s*, ^{t}Bu); 2.29 (*s*, *Me*C$_6$H$_4$); 2.46 (*m*, Me$_2$C*H*); 3.36 (*d*, ^2J = 13.0, 1 H, C$_6$H$_4$C*H*$_2$); 3.77 (*d*, ^2J = 14.1, 1 H, C$_6$H$_4$C*H*$_2$); 5.18 (*d*, ^3J = 6.9, Me$_2$CHC*H*); 6.03 (*s*, Cl$_2$CH); 6.82 (*s*, NH); 7.03–7.21 (*m*, 4 arom. H). ^{13}C-NMR (CDCl$_3$): 16.58 (1 Me of Me$_2$CH); 18.09 (1 Me of Me$_2$CH); 21.13 (*Me*C$_6$H$_4$); 27.69 (*Me*$_3$C); 31.23 (Me$_2$*C*H); 40.81 (C$_6$H$_4$*C*H$_2$); 57.54 (C(α)); 64.02 (Cl$_2$CH); 79.79 (Me$_2$CH*C*H); 86.05 (Me$_3$*C*); 116.05 (CN); 128.34, 129.62, 130.01, 138.54 (6 arom. C); 162.89 (CO); 163.92 (CO); 167.63 (CO).

3.3. *Other Synthesized Depsidipeptides.* They show physical data comparable to those given in *3.2.*

4. *Depsitripeptides* **9a**–**k**. 4.1. *General Procedure.* To a soln. of the amine in MeOH or CH$_2$Cl$_2$/MeOH 1:3, the aldehyde is added at 0° and the soln. stirred for 10 min. The acid in MeOH is added, followed, after 2 min, by **2** in a mixture of CH$_2$Cl$_2$ (3 ml) and MeOH (10 ml) (ester/aldehyde/amine/acid 1:1.5:1.5:1.5). After 2 h, the cooling bath is removed and the soln. stirred at r.t. for 2 days. The solvent is evaporated and AcOEt (10 ml) is added. The org. phase is washed twice with NaHSO$_3$ soln. (25 ml) and H$_2$O (25 ml), dried (Na$_2$SO$_4$), and evaporated. The obtained colorless oil is dissolved in Et$_2$O (10 ml) to give the diastereoisomers by crystallization. The mother liquor contains further product, which is accessible by CC (SiO$_2$, AcOEt/hexanes 9:1). Pure diastereoisomers were obtained after CC (SiO$_2$, MeOH/CH$_2$Cl$_2$ 2:1).

4.2. *Exemplary Data for Depsitripeptides.* tert-*Butyl α-Cyano-α-({2-[(dichloroacetyl)ethylamino]-3-methyl-1-oxobutyl}amino)-4-methylbenzenepropanoate* (**9f**). From *tert*-butyl α-cyano-α-isocyano-4-methylbenzenepropanoate (**2a**; 700 mg, 2.4 mmol) 2-methylpropanal (**4**; 259 mg, 3.6 mmol, 0.21 ml), 2M EtNH$_2$ (162 mg, 3.6 mmol, 1.8 ml) in MeOH and dichloroacetic acid (464 mg, 3.6 mmol, 0.73 ml) in MeOH (50 ml): 288 mg (25%) of a mixture of both diastereoisomers. M.p. 164°. IR (KBr): 3262*s*, 2968*s*, 2252*m*, 1750*s*, 1692*s*, 1649*s*, 1539*s*, 1443*m*, 1368*s*, 1151*s*, 1035*s*, 806*s*, 735*s*. ^{1}H-NMR (CDCl$_3$): 0.86, 0.89 (*d*, ^3J = 5.9, *Me*$_2$CH); 1.26 (*t*, ^3J = 6.9, *Me*CH$_2$N); 1.43 (*s*, ^{t}Bu); 2.34 (*s*, *Me*C$_6$H$_4$); 2.58 (*m*, Me$_2$C*H*); 3.30 (*d*, ^2J = 13.2, 1 H, C$_6$H$_4$C*H*$_2$); 3.42 (*d*, ^2J = 13.4, 1 H, C$_6$H$_4$C*H*$_2$); 3.47 (*m*, MeC*H*$_2$N); 3.89 (*d*, 1 H, ^3J = 6.5, Me$_2$CHC*H*); 6.25 (*s*, Cl$_2$CH); 7.13–7.26 (*m*, 4 arom. H); 7.86 (*s*, NH). ^{13}C-NMR (CDCl$_3$): 14.93, 15.16 (*Me*CH$_2$); 18.62, 18.87 (1 Me of Me$_2$CH), 19.60, 19.87 (1 Me of Me$_2$CH); 20.96, 21.14 (*Me*C$_6$H$_4$); 26.63, 26.96 (Me$_2$*C*H); 27.59, 27.67 (*Me*$_3$C); 39.97, 40.81 (Me*C*H$_2$N); 41.38, 41.53 (C$_6$H$_4$*C*H$_2$); 58.30, 58.69 (C(α)); 64.55, 64.70 (Cl$_2$CH); 76.21, 76.39 (Me$_2$CH*C*H); 85.00, 85.27 (^{t}Bu); 116.42, 116.52 (CN); 128.27, 128.46, 129.55, 129.62, 130.13, 130.29, 138.18, 138.29 (6 arom. C); 164.25, 164.38 (CO); 165.82, 165.87 (CO); 169.64, 169.76 (CO). MS: 240 (23.60, Cl$_2$CHCON(CH$_2$Me)CH-(CO)CH(Me$_2$), Cl$_2$CHCON(CH$_2$Me)CH(CO)CHMe$_2^+$, 212 (36.59, Cl$_2$CHCON(CH$_2$Me)CHCHMe$_2^+$), 105 (100, MeC$_6$H$_4$CH$_2^+$), 100 (23.94, COOCMe$_3^+$), 57 (62.96, C$_4$H$_9^+$). Anal. calc. for C$_{24}$H$_{35}$Cl$_2$N$_3$O$_5$: C 55.82, H 6.83, N 8.14; found: C 56.02, H 6.64, N 8.23.

After CC, one of the diastereoisomers is obtained in pure form: 140 mg (11%). M.p. 178°. ^{1}H-NMR (CDCl$_3$): 0.86 (*d*, ^3J = 5.7, Me$_2$CH); 1.25 (*t*, ^3J = 7.0, *Me*CH$_2$N); 1.42 (*s*, ^{t}Bu); 2.33 (*s*, *Me*C$_6$H$_4$); 2.57 (*m*, Me$_2$C*H*); 3.28 (*d*, ^2J = 13.4, 1 H, C$_6$H$_4$C*H*$_2$); 3.40 (*d*, ^2J = 13.3, 1 H, C$_6$H$_4$C*H*$_2$); 3.47 (*m*, MeC*H*$_2$N); 3.91 (*d*, ^3J = 6.6, Me$_2$CHC*H*); 6.25 (*s*, Cl$_2$CH); 7.12–7.25 (*m*, 4 arom. H); 7.87 (*s*, NH). ^{13}C-NMR (CDCl$_3$): 14.93 (*Me*CH$_2$N); 18.62 (1 Me of Me$_2$CH); 19.60 (1 Me of Me$_2$CH); 21.14 (*Me*C$_6$H$_4$); 26.63 (Me$_2$CH); 27.59 (*Me*$_3$C); 40.81 (Me*C*H$_2$N); 41.53 (C$_6$H$_4$*C*H$_2$); 58.30 (C(α)); 64.55 (Cl$_2$CH); 76.21 (Me$_2$CH*C*H); 85.27 (Me$_3$*C*); 116.52 (CN); 128.27, 129.55, 130.29, 138.18 (arom. C); 164.25 (CO); 165.87 (CO); 169.76 (CO).

4.3. *Other Synthesized Depsitripeptides.* They show physical data comparable to those given in *4.2.*

5. rel-*(2*R*)*-N-*[(1*R*)-2-(4-Chlorophenyl)-1-cyanoethyl]-2-[(dichloroacetyl)methylamino]-3-methylbutanamide* (**10**). Ethyl α-cyano-α-({2-[(dichloroacetyl)methylamino]-3-methyl-1-oxobutyl}amino)-chlorobenzenepropanoate (**9h**; 500 mg, 1.1 mmol) in acetone (50 ml) is treated with 5% aq. HCl soln. (20 ml) at 0° for 1 h. The soln. is neutralized and extracted with Et_2O (3×50 ml), the extract dried (Na_2SO_4) and evaporated, and the obtained mixtures of two diastereoisomers (364 mg, 80%) submitted to fractional crystallization from EtOH: 117 mg (39%) of pure **10**. Colorless platelets. M.p. 138°. IR (KBr): 3260*s*, 2965*s*, 2249*m*, 1761*s*, 1687*s*, 1652*s*, 1541*m*, 1418*s*, 1260*m*, 1142*s*, 1092*s*, 1017*m*, 888*m*, 807*m*. ^{1}H-NMR ($CDCl_3$): 1.02 (*d*, $^3J = 6.13$, *Me*$_2$CH); 2.06 (*m*, Me$_2$C*H*); 3.16 (*s*, MeN); 3.16 (*d*, $^2J = 12.38$, 1 H, $ClC_6H_4CH_2$); 3.13 (*m*, CHCN); 3.18 (*d*, $^2J = 12.79$, 1 H, $ClC_6H_4CH_2$); 4.81 (*d*, $^3J = 6.48$, Me_2CHCH); 6.09 (*s*, Cl_2CH); 7.21–7.68 (*m*, 4 arom. H); 8.76, 8.81 (2*s*, NH). ^{13}C-NMR ($CDCl_3$): 17.93 (1 Me of Me_2CH); 18.14 (1 Me of Me_2CH); 31.16 (Me_2CH); 32.29 (MeN); 35.87 (*C*HCN); 40.14 ($ClC_6H_4CH_2$); 58.23 (Me_2CHCH); 68.22 (Cl_2CH); 121.96 (CN); 127.29–132.03 (6 arom. C); 163.11 (CO); 163.38 (CO). MS: 405 (1.38, M^+), 224 (13.09, $Cl_2CHCON(Me)CH(CO)CHMe_2$), 196 (100.0, $Cl_2CHCONCHCHCHMe_2^+$), 125 (21.04, Cl_2CHCON^+), 83 (27.03, Cl_2CH^+). Anal. calc. for $C_{17}H_{20}{}^{35}Cl_3N_3O_2$: C 50.45, H 5.00, N 10.38; found: C 50.51, H 4.89, N 10.45.

For crystallographic data of **10**, see *Table 7*.

Table 7. *Crystallographic Data of* **10**

Formula	$C_{17}H_{20}Cl_3N_3O_2$
Molecular mass	404.73
Crystal description	platelet
Crystal size/mm	$0.30 \times 0.20 \times 0.05$
Crystal system	triclinic
Space group	$P\bar{1}$ (#2)
a/Å	11.025(5)
b/Å	11.821(5)
c/Å	18.022(5)
α/°	80.54(3)
β/°	80.12(1)
γ/°	62.26(1)
V/Å^3	2039(1)
Z	4
D_{calc}/g·cm^{-3}	1.319
F_{000}/e	840
μ(MoK_a)/cm^{-1}	4.642
Radiation	μ(MoK_a) (λ 0.7107 Å)
Scanning technique	ω-2θ
Unique reflections measured	8001 up to $(\sin\theta/\lambda)_{max} = 0.62$ Å^{-1}
Structure solution	direct methods (SIR)
H-Atoms	located and refined isotropically
Refinement: full-matrix least-squares, function minimized	$\Sigma w(\Delta F)^2$
Anomalous dispersion	all non-H-atoms[a])
Observed refls. included	4518 with $I \geq 3.0\sigma(I)$
Parameters refined	539
R	0.053[b])
R_w	0.057[b])
Convergence, largest shift $(\Delta/\sigma)_{max}$	0.08
High peak in final diff. map. $(\Delta\rho)_{max}$/e·Å^3	0.35(5)

[a]) Scattering factors and anomalous dispersion corrections were taken from [11].

[b]) $R = \dfrac{\sum ||F_{ibs}| - |F_{calc}||}{\sum |F_{obs}|}$, $R_w = \sqrt{\dfrac{\sum w||F_{obs}| - |F_{calc}||^2}{\sum w|F_{obs}|^2}}$, $w = [\delta(F)^2 + (0.03F_{obs})^2]^{-1}$

REFERENCES

[1] M. Bergemann, R. Neidlein, *Synthesis* **1996**, 975.
[2] M. Bergemann, R. Neidlein, *Synthesis* **1998**, 1437.
[3] M. Bergemann, R. Neidlein, *Helv. Chim. Acta* **1999**, *82*, 909.
[4] M. Passerini, *Gazz. Chim. Ital.* **1921**, *51II*, 126; M. Passerini, *Gazz. Chim. Ital*. **1921**, *51II*, 181.
[5] I. Ugi, *Angew. Chem*. **1982**, *94*, 826.
[6] M. Passerini, *Gazz. Chim. Ital*. **1925**, *54*, 529; R. Neidlein, *Angew. Chem.* **1964**, *76*, 440; R. Neidlein, *Angew. Chem*. **1964**, *76*, 500; J. W. McFarland, *J. Org. Chem*. **1963**, *28*, 2179; R. Neidlein, *Arch. Pharm*. **1966**, *299*, 603; R. H. Baker, A. H. Schlesinger, *J. Am. Chem. Soc*. **1945**, *67*, 1499; R. H. Baker, D. Stanonis, *J. Am. Chem. Soc*. **1951**, *73*, 699.
[7] I. Ugi, C. Steinbrückner, *Chem. Ber*. **1961**, *94*, 734; I. Ugi, 'Isonitrile Chemistry', Academic Press, New York-London, 1971, 145.
[8] I. Ugi, *J. Prakt. Chem*. **1997**, *339*, 499.
[9] I. Ugi, D. Marquarding, R. Urban, 'Chemistry and Biochemistry of Amino Acids, Peptides and Proteins', Vol. 6, New York, 1982, p. 245.
[10] I. Ugi, G. Kaufhold, *Justus Liebigs Ann. Chem*. **1967**, *709*, 11.
[11] 'International Tables for X-Ray Crystallography', Vol. IV, Kynoch Press, Birmingham, England, 1974.

Received November 26, 2001