Reactions of *N*-Acyl-*N*-(2,2,2-trichloroethylidene)amines with Enamines

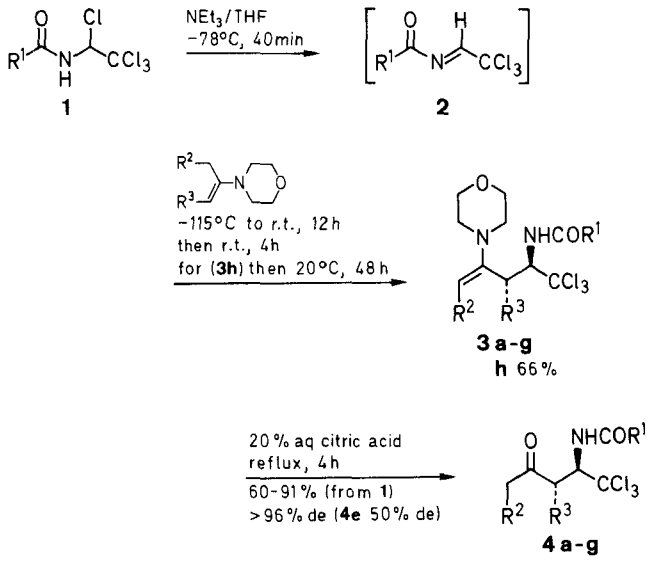
Wolfgang Miltz, Wolfgang Steglich*

Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Straße 1, D-5300 Bonn 1, Federal Republic of Germany

Dedicated to Prof. Dr. Dr. h.c. H.J. Bestmann on the occasion of his 65th birthday

The reaction of *N*-acyl-*N*-(2,2,2-trichloroethylidene)amines with cyclic enamines affords chiral 2,2,2-trichloroethyl amine derivatives with high diastereo- and enantioselectivity.

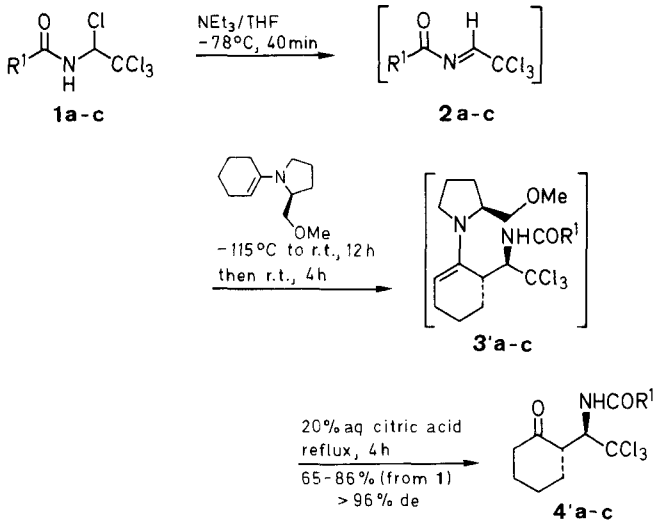
The reaction of *N*-acylimino acetates with cyclic enamines yields α-amino-γ-oxocarboxylic acid derivatives with excellent diastereoselectivity.[1] In this paper we report an extension of this reaction to *N*-acyl-*N*-(2,2,2-trichloroethylidene)amines **2** which can be easily obtained *in situ* from *N*-acyl-1,2,2,2-tetrachloroethylamines **1** by treatment with triethylamine in tetrahydrofuran.[2] On addition of a carbocyclic enamine to this solution at −78 °C the α-amidoalkylated enamines **3** are formed with an excellent diastereoselectivity of 98:2. With exception of **3h** the intermediates **3** were directly hydrolyzed to the corresponding ketones **4** by treatment with aqueous citric acid (see below). Alternatively the enamines **3** may be further reacted with acylimines to yield bis-amidoalkylated products.[3]



3, 4	R^1	R^2	R^3	3, 4	R^1	R^2	R^3
a	Me	$-(CH_2)_3-$		**e**	Me	$-CH_2SCH_2-$	
b	Ph	$-(CH_2)_3-$		**f**	Me	$-(CH_2)_4-$	
c	BnO	$-(CH_2)_3-$		**g**	BnO	$-(CH_2)_4-$	
d	PhCH=CH	$-(CH_2)_3-$		**3h**	Ph	$-OC(CH_3)_2O-$	

According to prior results[1] the *anti*-configuration (2*S*,1′*R*/2*R*,1′S) can be assigned to the major diastereoisomer. In contrast to the acylimino acetates,[1] the reaction of *N*-acetyl-*N*-(2,2,2,-trichloroethylidene)amine with the enamine of thiopyranone gives only a poor diastereoselectivity of 75:25.

The asymmetric synthesis was carried out with (*S*)-1-(1-cyclohexenyl)-2-(methoxymethyl)pyrrolidine and ee-values of more than 90% were obtained (see below). In the case of compound **4a′** the enantiomeric excess was determined by ^{1}H-NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent and the methyl singlet as the characteristic signal. In the case of **4b′** recrystallization of the crude product yielded the main isomer with an ee-value of >98%. This was shown by analytical HPLC measurements with the chiral *Okamoto* phase.[4] Since both analytical methods failed in the case of **4c′**, the enantiomeric excess was determined by comparison of the optical rotation of the crude product with that of the recrystallized material. The absolute stereochemistry at the newly formed chiral centers can be assigned as (2*S*,1′*R*) in accord to the reaction of acylamino acetates with enamines.[1]



1–4′	R^1	ee (%)
a	Me	96
b	Ph	>98[a]
c	BnO	92

[a] After recrystallization.

Melting points were determined with a Büchi melting-point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 1420 spectrophotometer. The ^{1}H-NMR spectra were recorded with Varian EM 390 and Bruker WM 400 instruments (solutions in $CDCl_3$ unless otherwise stated, TMS as internal reference). Optical rotations were measured with a Perkin-Elmer 241 polarimeter. TLC separations were carried out on silica gel

Table. Aminoalkylated Ketones **4** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula	$[\alpha]_D^{20}$ (c, $CDCl_3$)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
4a	82	75–77	$C_{10}H_{14}Cl_3NO_2$	−33.27	3360, 2970–2860, 1705, 1670, 1510, 805, 790, 745, 640	1.6–2.5 (m, 8H), 2.06 (s, 3H), 3.33 (m, 1H), 4.8 (dd, 1H, J = 10, 0.9), 8.06 (d, 1H, J = 10)
4a′	65	88	(286.6)	(2)		
4b	71	121	$C_{15}H_{16}Cl_3NO$	+9.1	3400, 3320, 2950, 1700, 1670, 1640, 1510, 1480, 1310, 805, 790, 710	1.6–2.5 (m, 8H), 3.36 (m, 1H), 5.0 (dd, 1H, J = 10, 0.9), 7.36–7.5 (m, 3H), 7.73–7.9 (m, 2H), 8.93 (d, 1H, J = 10)
4b′	86	126	(332.6)	(2)		
4c	85	117	$C_{16}H_{18}Cl_3NO_3$	+4.3	3380, 2960, 2940, 2860, 1725, 1695, 1500, 1450, 1295, 1220, 1050, 805, 790, 750, 695	1.5–2.5 (m, 8H), 3.33 (m, 1H), 4.43 (d, 1H, J = 10), 5.11 (s, 1H), 5.13 (s, 1H), 7.3 (d, 1H, J = 10), 7.31 (s, 5H)
4c′	81	103	(378.7)	(2.25)		
4d	60	90–92	$C_{17}H_{18}Cl_3NO_2$ (374.7)		3360, 3280, 3050, 2930, 2850, 1710, 1660, 1630, 1490, 1200, 970, 800, 760	1.6–2.56 (m, 8H), 3.4 (m, 1H), 4.96 (dd, 1H, J = 9, 0.9), 6.46 (d, 1H, J = 15), 7.3–7.56 (m, 5H), 7.66 (d, 1H, J = 15), 8.23 (d, 1H, J = 9)
4e	85	94	$C_9H_{12}Cl_3NO_2S$	+5.2	3300, 3050, 2960, 2920, 1720, 1660, 1540, 1530, 1430, 1370, 1270, 1140, 1120, 1025, 810, 790, 750, 635	2.06 (s, 3H), 2.66–3.6 (m, 7H), 5.0 (dd, 1H, J = 10, 1.5), 7.76 (d, 1H, J = 10)
4e′	78	oil	(304.5)	(1)		
4f	91	87–88	$C_{11}H_{16}Cl_3NO_2$ (300.6)		3380, 2950, 2920, 2840, 1700, 1680, 1500, 1450, 1440, 1365, 1290, 1280, 1220, 1030, 780, 770, 650	1.1–2.1 (m, 8H), 2.1 (s, 3H), 2.33–2.86 (m, 2H), 3.6–3.76 (m, 1H), 4.9 (dd, 1H, J = 9, 2), 7.93 (d, 1H, J = 9)
4g	83	98	$C_{17}H_{22}Cl_3NO_3$ (394.7)		3380, 2920, 2850, 1725, 1690, 1500, 1450, 1290, 1280, 1260, 1220, 1125, 1050, 1030, 810	1.0–2.1 (m, 8H), 2.2–2.86 (m, 2H), 3.56–3.76 (m, 1H), 4.6 (dd, 1H, J = 10, 2), 5.1 (s, 2H), 7.26 (br d, 1H, J = 9), 7.3 (s, 5H)

TLC plates Merck 60 F_{254}. Organic solutions were dried ($MgSO_4$) and solvent evaporation was carried out at reduced pressure using a rotatory evaporator. All air- and moisture-sensitive reactions were conducted in a flame-dried Schlenk apparatus under an atmosphere of dry Ar. Elemental analyses were performed at the Institut für Organische Chemie und Biochemie, Universität Bonn.

_N_-Acyl-1,2,2,2-tetrachloroethylamines 1:
Compounds **1** are obtained by heating a mixture of the corresponding 1-hydroxy compound and PCl_5 according to Lit.[2]

2,2-Dimethyl-5-morpholino-4_H_-1,3-dioxin:
This compound is obtained in 87% yield from 2,2-dimethyl-1,3-dioxan-5-one[5] by treatment with two equiv of 4-(trimethylsilyl)-morpholine[6] for 12 h at 80 °C in a closed reaction vessel and subsequent Kugelrohr distillation; bp 80 °C/0.025 Torr.

4-(1-Benzoylamino-2,2,2-trichloroethyl)-2,2-dimethyl-5-morpholino-4_H_-1,3-dioxin (3h):
To a solution of _N_-benzoyl-1,2,2,2-tetrachloroethylamine (**1b**; 3.13 g, 10.9 mmol) in dry THF (40 mL) at −78 °C (dry ice/EtOH) is added dropwise Et_3N (1.5 mL, 11 mmol). The suspension is stirred for 40 min at −78 °C. After filtration through Celite, the filtrate is cooled to −115 °C by adding liquid N_2 to the cooling bath, and a solution of 2,2-dimethyl-5-morpholino-4_H_-1,3-dioxin (1.2 g, 6 mmol) in dry THF (5 mL) is introduced via syringe. The mixture is allowed to warm to r.t. overnight (12 h) with stirring which is continued for additional 48 h at 20 °C. The solvent is then removed *in vacuo* and the crude product is purified by recrystallization from EtOAc/petroleum ether (bp 40–60 °C); yield: 1.61 g (66%); mp 120 °C.

$C_{19}H_{23}Cl_3N_2O_4$ calc. C 50.74 H: 5.15 N: 6.23
found 50.59 5.11 6.07

IR (KBr): ν = 3240, 2940, 2860, 1675, 1515, 1485, 1450, 1380, 1365, 1310, 1260, 1200, 1180, 1140, 1120, 890, 875, 785, 715 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.46 (s, 3H), 1.51 (s, 3H), 2.27 (t, J = 5 Hz, 1H), 2.4 (t, 1H, J = 5 Hz), 2.94 (t, 1H, J = 5 Hz), 3.06 (t, 1H, J = 5 Hz), 3.68 (t, 4H, J = 5 Hz), 4.83 (dd, 1H, J = 3, 2 Hz), 5.58 (dd, 1H, J = 10, 3 Hz), 6.18 (d, 1H, J = 2 Hz), 7.44–7.57 (m, 3H), 7.77–7.88 (m, 2H), 8.38 (br d, 1H, J = 10 Hz).

^{13}C-NMR ($CDCl_3$/TMS): δ = 22.49, 26.54, 51.82, 67.03, 67.29, 68.65, 99.20, 101.99, 126.29, 127.27, 127.46, 128.79, 128.95, 132.22, 133.48, 134.22, 167.14.

Amidoalkylated Ketones 4; General Procedure:
The acylimine **2** is formed by addition of Et_3N (0.75 mL, 5.5 mmol) to a solution of **1** (5 mmol) in dry THF (20 mL) at −78 °C (dry ice/EtOH). The suspension is stirred for 40 min at this temperature and then cooled to −115 °C by addition of liquid N_2 to the cooling bath. A solution of the enamine (6 mmol) in dry THF (5 mL) is added very slowly via syringe, and the mixture is allowed to warm up slowly to r.t. overnight (12 h). After continued stirring for 4 h, the reaction mixture is quenched with 20% aq citric acid (10 mL) and refluxed for 4 h. After addition of EtOAc (50 mL), the aq layer is neutralized with sat $NaHCO_3$ solution and separated. The organic layer is washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product can be purified by recrystallization from EtOAc/petroleum ether (bp 40–60 °C).

Received: 25 May 1990

(1) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron Lett.* **1985**, *41*, 1693.
(2) Weygand, F.; Steglich, W.; Lengyel, I.; Fraunberger, F.; Meierhofer, A.; Oettmeier, W. *Chem. Ber.* **1966**, *99*, 1944.
(3) Miltz, W. *Ph. D. Thesis*, University of Bonn, 1988.
(4) Okamoto, Y.; Kowashima, M.; Hatada, K. *J. Chromat.* **1986**, *363*, 173.
(5) Araki, Y.; Nagasawa, J.; Ishido, Y. *J. Chem. Soc., Perkin Trans.* **1981**, 12.
(6) Pike, R.A.; Schank, R.L. *J. Org. Chem.* **1962**, *27*, 2190.