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Synthesis of Bis-(3,5)pyrazolophanes by Sequential Intermolecular-Intramolecular Nitrilimine Cycloadditions

Gianluigi Broggini, Luisa Garanti, Giorgio Molteni and Gaetano Zecchi*

Dipartimento di Chimica Organica e Industriale dell'Università di Milano,

Via Golgi 19, 20133 Milano, Italy

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Abstract: A series of bis-(3,5)pyrazolophanes of potential interest in supramolecular chemistry have been synthesized by exploiting sequential intermolecular-intramolecular cycloadditions of properly functionalised nitrilimines.

A number of papers are available describing the construction of macrocyclic systems through intramolecular cycloadditions of 1,3-dipoles such as nitriloxides,[1-5] nitrilimines,[6] azides,[7] nitrones,[8] azomethinylides,[9,10] and carbonylylides.[11] Our recent contributions in this field[6] are concerned with the use of suitably functionalised nitrilimines as precursors of (1,5)pyrazolophanes. We now wish to report a version of the same methodology leading to mono- and bis-(3,5)pyrazolophanes. Such kind of molecules are receiving attention as non-conventional ligands towards metal cations.[12]

Results

We explored the behaviour of two types of nitrilimines, namely **5** and **15**, which differ in the nature of the tether joining the dipole and dipolarophile groups (Schemes 1 and 2). All of them were generated *in situ* upon basic treatment of the corresponding hydrazonyl chlorides (*i.e.* **4** and **14**, respectively), the synthesis of which was accomplished as outlined in Schemes 1 and 2.

In order to generate the desired nitrilimines, compounds **4** and **14** were treated with silver carbonate in dioxane at room temperature. Schemes 1 and 2 illustrate the complex reaction outcomes, while detailed data are collected in Tables 1 and 2. The intermediate species **8a-e** and **17c** were really isolated when stopping the reaction at short times and were proven to be the precursors of the macrocyclic products **10a-e** and **18c**, respectively. In the case of compounds **10** and **18** containing two stereocentres, we assigned a chiral structure rather than a mesoform one whenever the NMR signal of the 4-pyrazolinic protons was splitted in the presence of $Eu(hfc)_3$ [tris{heptafluoropropylhydroxymethylene-(+)-camphorato}europium-(III)].

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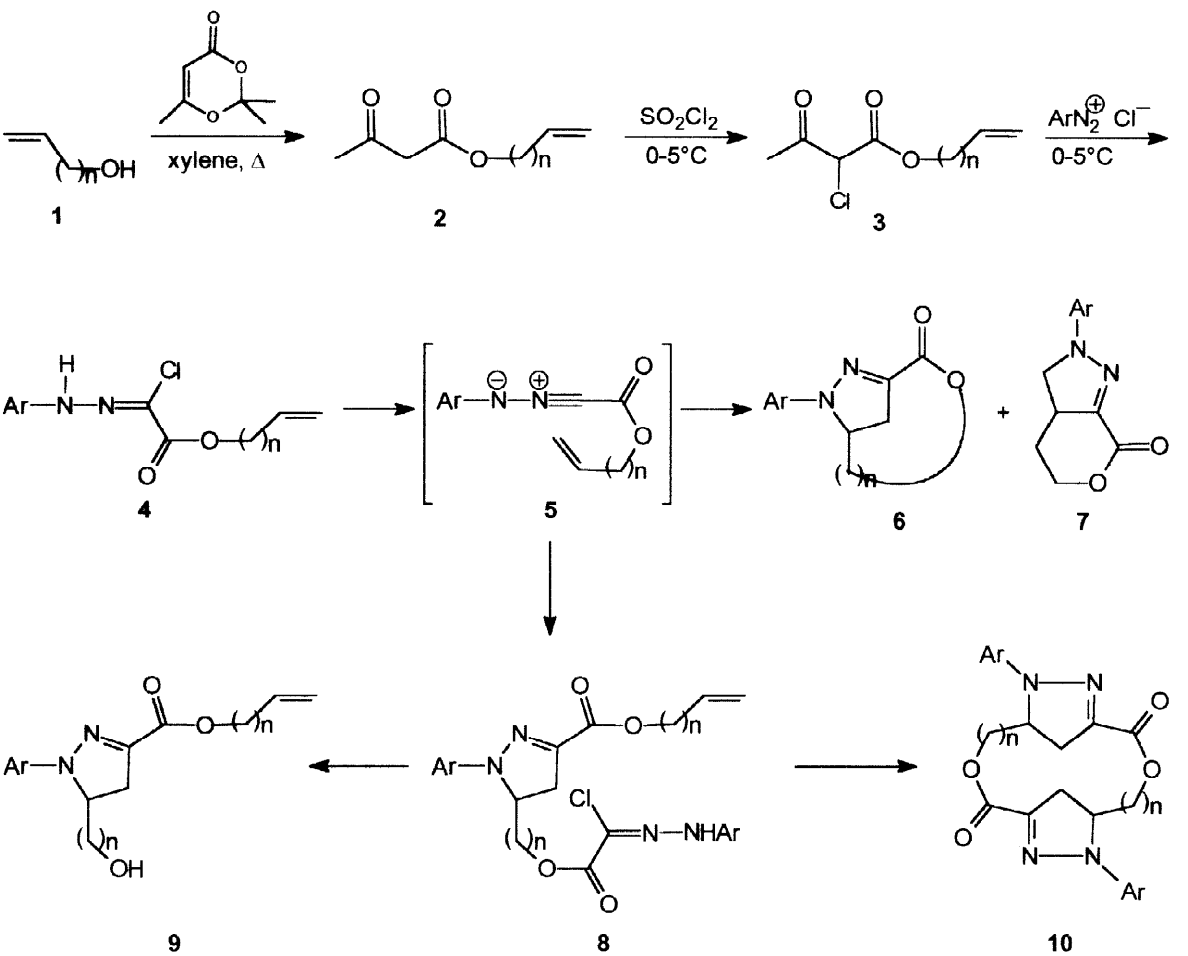
Table 1. Reaction of **4** with silver carbonate in dioxane at room temperature.

Entry	Time (h)	Products and yields (%)				Eluant[a]
		6	**7**	**9**	**10**	
a	185	–	9	–	20[b]	AcOEt/LP 1:2
b	160	–	–	5	2[b] 6[c]	AcOEt/LP 1:1
c	100	–	–	–	20[b] 20[c]	AcOEt/LP 2:1
d	112	6	–	8	30[b]	CH_2Cl_2/LP 5:1
e	170	12	–	10	30[b]	Et_2O/LP 1:2

[a]LP = light petroleum b.p. 40-60°C. [b]Racemic. [c]Meso form.

Scheme 1



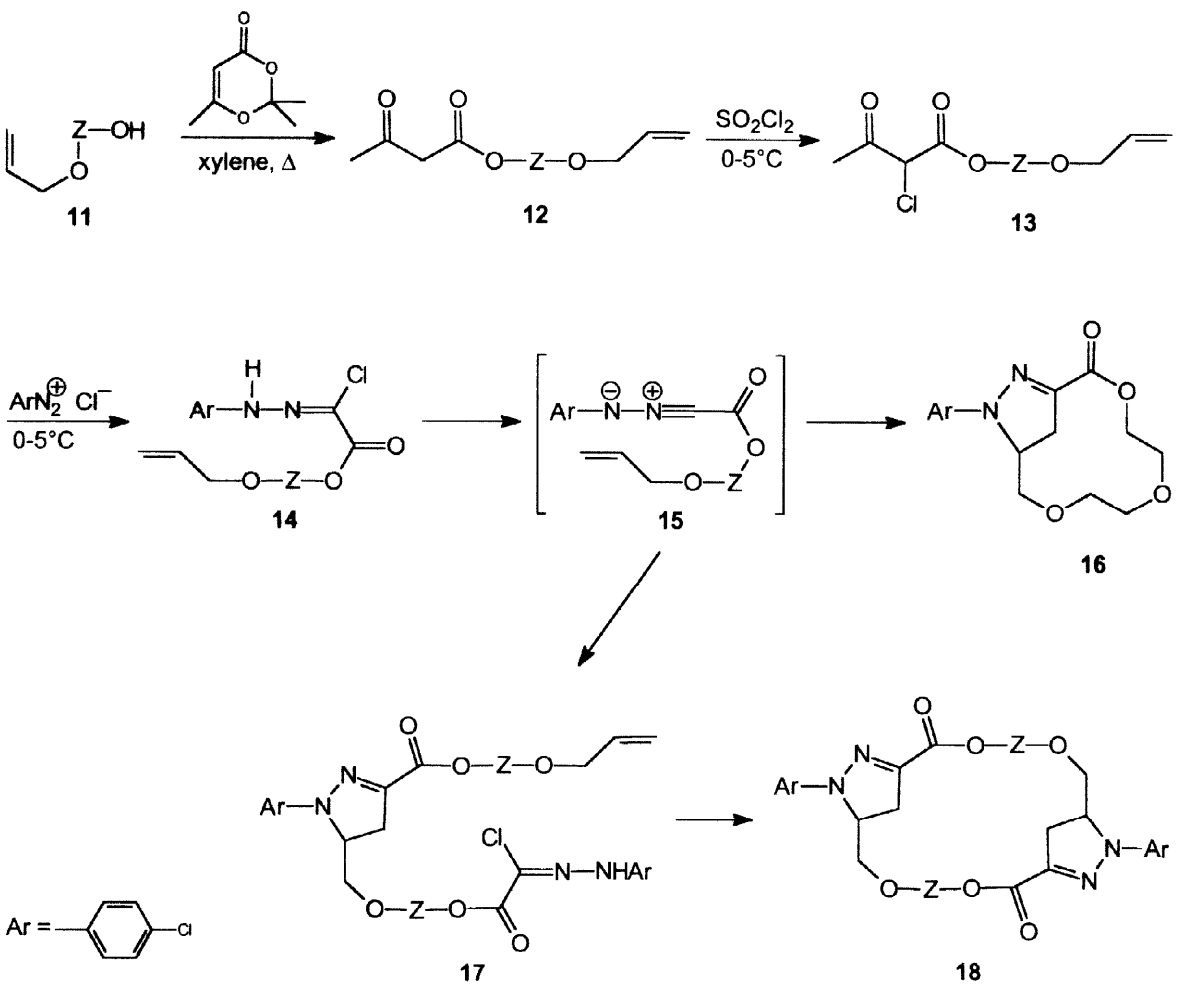
Entry	**a**	**b**	**c**	**d**	**e**
n	2	3	4	8	9

Table 2. Reaction of **14** with silver carbonate in dioxane at room temperature.

Entry	Time (h)	Products and yields (%)		Eluant
		16	**18**	
a	48	–	12[a] 12[b]	AcOEt/Et_2O 1:5
b	54	–	25[a]	Et_2O
c	120	18	10[c]	AcOEt/Et_2O 1:3

[a]Racemic. [b]Meso form. [c]Mixture of the two diastereoisomers not separated.

Scheme 2



Entry	a	b	c
Z	$-CH_2CH_2-$		$-CH_2CH_2OCH_2CH_2-$

Discussion

The above results reveal a very interesting trend. It has been amply shown that, in nitrilimine cycloadditions to terminal alkenes, electronic factors favour the formation of 4-unsubstituted over 5-unsubstituted pyrazole derivatives.[13-15] In our present case, this rule is just obeyed in intermolecular processes (**5a-e** → **8a-e** and **15a-c** → **17a-c**) and also in intramolecular processes provided that the tether between the reactive centers is long and flexible enough to permit the formation of bridged-ring structures (**8a-e** → **10a-e**, **17a-c** → **18a-c**, **5d,e** → **6d,e**, and **15c** → **16**). On these grounds, one can readily explain the lack of formation of the intramolecular cycloadducts **6a-c** and **16a,b**. On the other hand, the reversed orientation leading to a 5-unsubstituted pyrazole ring becomes operative only if a favourable proximity effect[16] intervenes to circumvent the impervious enthalpic barrier (**5a** → **7**).

The peculiar role of silver carbonate as basic agent remains to be underlined. In a previous paper,[17] we reported that the reaction of hydrazonyl chlorides **4a,b** with triethylamine did no characterisable cycloadduct, but only resinous material. It is reasonable to think that the insolubility of Ag_2CO_3 in dioxane determines a very slow generation of the nitrilimine species. Consequently, the latter happens to react under high dilution conditions, which are well-known to favour the intramolecular processes leading to macrocyclic structures.[18-20]

Experimental Section

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra (in nujol unless otherwise stated) were recorded with a Perkin-Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H-NMR spectra were taken with a Bruker AC 300 instrument (in $CDCl_3$ solutions unless otherwise stated). Chemical shifts are given as ppm from tetramethylsilane and coupling constant are given in Hz.

Compounds **1a-e** are commercially available. Compounds **2a,b**,[17] **3a,b**,[17] **4a,b**,[17] **11a**,[21] **11b**,[22] and **11c**[23] are already known in the literature.

General procedure for the preparation of alkenyl acetoacetates 2a-e and 12a-c. A solution of the alkenol **1** or **11** (0.1 mol) in xylene (20 mL) was treated with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (14.2 g, 0.1 mol). The mixture was refluxed for 1.5h. Evaporation of the solvent under reduced pressure and subsequent *in vacuo* distillation of the residue gave the acetoacetates **2a-e** as analytically pure samples. Compounds **12** were otherwise obtained as undistillable thick oils and used without further purification.

2c (16.4 g, 89% yield) b.p. 88°C (3 mmHg); IR (neat): 1750, 1720 (cm^{-1}); ^{1}H-NMR: 1.00-2.00 (6H, m), 2.19 (3H, s), 3.35 (2H, s), 4.10 (2H, t, *J*=6.8), 4.82-5.08 (2H, m), 5.52-6.02 (1H, m); MS: *m/z* 184 (M$^+$). Anal Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.23, H, 8.80.

2d (20.4 g, 85% yield) b.p. 106°C (1 mmHg); IR (neat): 1740, 1720 (cm^{-1}); ^{1}H-NMR: 1.10-2.10 (14H, m), 2.20 (3H, s), 3.37 (2H, s), 4.08 (2H, t, *J*=6.5), 4.70-5.10 (2H, m), 5.50-6.10 (1H, m); MS: *m/z* 240 (M$^+$). Anal Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.02, H, 10.10.

2e (22.9 g, 90% yield) b.p. 118°C (1 mmHg); IR (neat): 1750, 1730 (cm^{-1}); ^{1}H-NMR: δ 1.15-2.10 (16H, m), 2.24 (3H, s), 3.42 (2H, s), 4.10 (2H, t, *J*=5.9), 4.80-5.12 (2H, m), 5.55-6.08 (1H, m); MS: ***m/z*** **254** (M^+). Anal. Calcd for $C_{15}H_{24}O_3$: C, 70.83; H, 10.30. Found: C, 70.90; H, 10.34.

12a (13.0 g, 70% yield); IR (neat): 1750, 1720 (cm^{-1}); ^{1}H-NMR: δ 2.25 (3H, s), 3.47 (3H, s), 3.65 (2H, t, *J*=5.2), 4.00 (2H, dt, *J*=5.9, 1.3), 4.27 (2H, t, *J*=5.2), 5.10-5.40 (2H, m), 5.60-6.12 (1H, m); MS: *m/z* 186 (M^+).

12b (14.5 g, 62% yield); IR (neat): 1760, 1720 (cm^{-1}); ^{1}H-NMR: δ 2.36 (3H, s), 3.66 (2H, s), 4.55 (2H, dt, *J*=5.1, 1.3), 5.18-5.38 (2H, m), 5.77-6.24 (1H, m), 6.80-7.30 (4H, m); MS: *m/z* 234 (M^+).

12c (13.3 g, 58% yield); IR (neat): 1745, 1720 (cm^{-1}); ^{1}H-NMR: δ 2.23 (3H, s), 3.45 (2H, s), 3.50-3.80 (6H, m), 4.00 (2H, dt, *J*=5.8, 1.0), 4.28 (2H, t, *J*=4.9), 4.95-5.40 (2H, m), 5.65-6.15 (1H, m); MS: *m/z* 230 (M^+).

General procedure for the preparation of alkenyl chloroacetoacetates 3a-e and 13a-c. A solution of sulfuryl chloride (8.37 g, 62 mmol) in dry chloroform (100 mL) was slowly added (1h) to a solution of **2** or **12** (50 mmol) in dry chloroform (50 mL), on keeping the temperature in the range 0-5°C. After 2h at room temperature, chloroform (100 mL) was added and the organic solution was washed with 5% aqueous sodium hydrogencarbonate (50 mL). The organic layer was then washed with water (150 mL) and dried over sodium sulfate. The solvent was removed and the residue was distilled *in vacuo* to give pure chloroacetacetates **3**. Compounds **13** was otherwise obtained as undistillable thick oils which were used without further purification.

3c (10.5 g, 96% yield) b.p. 90°C (3 mmHg); IR (neat): 1770, 1750 (cm^{-1}); ^{1}H-NMR: δ 1.20-2.20 (6H, m), 2.35 (3H, s), 4.22 (2H, t, *J*=6.8), 4.72 (1H, s), 4.90-5.12 (2H, m), 5.55-6.02 (1H, m); MS: *m/z* 218 (M^+). Anal. Calcd for $C_{10}H_{15}ClO_3$: C, 54.92; H, 6.91; Cl, 16.21. Found: C, 55.00; H, 6.97; Cl, 16.33.

3d (6.85 g, 50% yield) b.p. 75°C (2 mmHg); IR (neat): 1760, 1740 (cm^{-1}); ^{1}H-NMR: δ 1.15-2.12 (14H, m), 2.35 (3H, s), 4.18 (2H, t, *J*=6.0), 4.71 (1H, s), 4.80-5.10 (2H, m), 5.50-6.05 (1H, m); MS: *m/z* 274 (M^+). Anal. Calcd for $C_{14}H_{23}ClO_3$: C, 61.19; H, 8.44; Cl, 12.90. Found: C, 61.11; H, 8.40; Cl, 13.02.

3e (6.0 g, 42% yield) b.p. 75°C (2 mmHg); IR (neat): 1760, 1740 (cm^{-1}); ^{1}H-NMR: δ 1.15-2.15 (16H, m), 2.38 (3H, s), 4.18 (2H, t, *J*=5.9), 4.72 (1H, s), 4.78-5.11 (2H, m), 5.55-6.08 (1H, m); MS: *m/z* 288 (M^+). Anal. Calcd for $C_{15}H_{25}ClO_3$: C, 62.38; H, 8.72; Cl, 12.28. Found: C, 62.43; H, 8.77; Cl, 12.37.

13a (4.5 g, 41% yield); IR (neat): 1770, 1740 (cm^{-1}); ^{1}H-NMR: δ 2.40 (3H, s), 3.65 (2H, t, *J*=5.2), 4.05 (2H, dt, *J*=5.2, 1.3), 4.45 (2H, t, *J*=5.2), 4.80 (1H, s), 5.02-5.38 (2H, m), 5.65-6.15 (1H, m); MS: *m/z* 220 (M^+).

13b (11.0 g, 82% yield); IR (neat): 1780, 1730 (cm^{-1}); ^{1}H-NMR: δ 2.45 (3H, s), 4.55 (2H, dt, *J*=5.1, 1.1), 5.00 (1H, s), 5.18-5.45 (2H, m), 5.72-6.15 (1H, m), 6.80-7.30 (4H, m); MS: *m/z* 268 (M^+).

13c (11.9 g, 90% yield); IR (neat): 1770, 1740 (cm^{-1}); ^{1}H-NMR: δ 2.35 (3H, s), 3.50-3.80 (6H, m), 4.00 (2H, dt, *J*=5.8, 1.0), 4.35 (2H, t, *J*=4.9), 4.78 (1H, s), 5.02-5.38 (2H, m), 5.65-6.15 (1H, m); MS: *m/z* 264 (M^+).

General procedure for the preparation of hydrazonyl chlorides 4a-e and 14a-c. A cold aqueous solution of 4-chlorobenzenediazonium chloride (25 mmol) was added dropwise to a solution of **3** or **13** (25 mmol) in 80% aqueous methanol (65 mL) under vigorous stirring and ice-cooling. During the addition, the pH was adjusted to 5 by adding sodium acetate. The mixture was allowed to stand overnight under stirring at room temperature. The solvent was partly removed under reduced pressure and the resulting mixture was extracted with diethyl ether (100 mL). The organic layer was washed firstly with 5% sodium hydrogencarbonate (50 mL), then with water (150 mL), and dried over sodium sulfate. Evaporation of the solvent gave solid and subsequent recrystallisation with diisopropylether gave the hydrazonyl chlorides **4** or **14** in the pure state.

4c (2.04 g, 26% yield) m.p. 83°C; IR: 3260, 1710 (cm-1); 1H-NMR: (1.42-2.30 (6H, m), 4.32 (2H, t, *J*=6.5), 4.85-5.20 (2H, m), 5.55-6.15 (1H, m), 6.88-7.52 (4H, m), 8.25 (1H, br s); MS: *m/z* 314 (M^+). Anal. Calcd for $C_{14}H_{16}Cl_2N_2O_2$: C, 53.35; H, 5.12; Cl, 22.50; N, 8.89. Found: C, 53.28; H, 5.16; Cl, 22.62; N, 8.96.

4d (4.90 g, 53% yield) m.p. 68°C; IR: 3260, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.10-2.20 (14H, m), 4.28 (2H, t, *J*=6.5), 4.78-5.10 (2H, m), 5.50-6.10 (1H, m), 7.05-7.40 (4H, m), 8.25 (1H, br s); MS: *m/z* 370 (M^+). Anal. Calcd for $C_{18}H_{24}Cl_2N_2O_2$: C, 58.23; H, 6.51; Cl, 19.10; N, 7.54. Found: C, 58.31; H, 6.59; Cl, 19.21; N, 7.60.

4e (2.88 g, 30% yield) m.p. 68°C; IR: 3260, 1715 (cm^{-1}); ^{1}H-NMR: δ 1.15-2.10 (16H, m), 4.30 (2H, t, *J*=6.7), 4.80-5.05 (2H, m), 5.55-6.08 (1H, m), 7.03-7.38 (4H, m), 8.30 (1H, br s); MS: *m/z* 384 (M^+). Anal. Calcd for $C_{19}H_{26}Cl_2N_2O_2$: C, 59.22; H, 6.80; Cl, 18.40; N, 7.27. Found: C, 59.28; H, 6.76; Cl, 18.30; N, 7.24.

14a (3.63 g, 46% yield) m.p. 84°C; IR: 3260, 1715 (cm^{-1}); ^{1}H-NMR: δ 3.75 (2H, t, *J*=5.1), 4.07 (2H, dt, *J*=5.2, 1.0), 4.46 (2H, t, *J*=5.1), 5.10-5.45 (2H, m), 5.67-6.20 (1H, m), 7.05-7.40 (4H, m), 8.30 (1H, br s); MS: *m/z* 316 (M^+). Anal. Calcd for $C_{13}H_{14}Cl_2N_2O_3$: C, 49.23; H, 4.45; Cl, 22.36; N, 8.83. Found: C, 49.28; H, 4.39; Cl, 22.30; N, 8.72.

14b (3.19 g, 35% yield) m.p. 110°C; IR: 3260, 1730 (cm^{-1}); ^{1}H-NMR: δ 4.58 (2H, dt, *J*=5.0, 1.4), 5.22 (2H, dd, *J*=10.6, 1.3), 5.37 (1H, dd, *J*=17.3, 1.3), 5.68-6.13 (1H, m), 6.99-7.23 (8H, m), 8.44 (1H, br s); MS: *m/z* 364 (M^+). Anal. Calcd for $C_{17}H_{14}Cl_2N_2O_3$: C, 55.91; H, 3.86; Cl, 19.41; N, 7.67. Found: C, 56.00; H, 3.92; Cl, 19.50; N, 7.70.

14c (4.77 g, 53% yield) m.p. 65°C; IR: 3240, 1720 (cm^{-1}); ^{1}H-NMR: δ 3.48-3.88 (6H, m), 4.00 (2H, dt, *J*=5.8, 1.0), 4.45 (2H, t, *J*=4.9), 5.03-5.38 (2H, m), 5.62-6.15 (1H, m), 7.05-7.38 (4H, m), 8.33 (1H, br s); MS: *m/z* 360 (M^+). Anal. Calcd for $C_{15}H_{18}Cl_2N_2O_4$: C, 49.88; H, 5.02; Cl, 19.63; N, 7.76. Found: C, 49.78; H, 4.98; Cl, 19.56; N, 7.69.

General procedure for the reaction of hydrazonyl chlorides 4 and 14 with silver carbonate in dioxane. A solution of the hydrazonyl chlorides **4** or **14** (10 mmol) in dry dioxane (500 mL) was treated with silver carbonate (5.52 g, 20 mmol), and stirred in the dark at room temperature for the time indicated in Tables 1 and 2. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column. Eluents, products and isolation yields are collected in Tables 1 and 2. All compounds were obtained in analytically pure state by recrystallisation.

6d (0.20 g, 6% yield) m.p. 149°C (from methanol); IR: 1720 (cm^{-1}); ^{1}H-NMR: δ 1.20-1.80 (14H, m), 3.13 (1H, dd, *J*=16.6, 4.2), 3.22 (1H, dd, *J*=16.6, 10.3), 4.30-4.60 (2H, m), 4.70-4.80 (1H, m), 7.10-7.30 (4H, m); MS: *m/z* 334 (M^+). Anal. Calcd for $C_{18}H_{23}ClN_2O_2$: C, 64.57; H, 6.92; Cl, 10.59; N, 8.37. Found: C, 64.63; H, 6.98; Cl, 10.65; N, 8.42.

6e (0.42 g, 12% yield) m.p. 157°C (from methanol-diisopropylether); IR: 1715 (cm^{-1}); ^{1}H-NMR: δ 1.20-1.70 (16H, m), 3.08 (1H, dd, *J*=17.5, 3.3), 3.27 (1H, dd, *J*=17.5, 11.7), 4.36 (1H, ddd, *J*=11.7, 6.7, 3.7), 4.53 (1H, ddd, *J*=11.7, 7.5, 3.7), 4.68-4.77 (1H, m), 7.10-7.25 (4H, m); MS: *m/z* 348 (M^+). Anal. Calcd for $C_{19}H_{25}ClN_2O_2$: C, 65.41; H, 7.22; Cl, 10.16; N, 8.03. Found: C, 65.35; H, 7.25; Cl, 10.24; N, 8.11.

7 (0.23 g, 9% yield) m.p. 147°C (from hexane-benzene); IR: 1720 (cm^{-1}); ^{1}H-NMR: δ 2.04-2.37 (2H, m), 3.62 (1H, dd, *J*=16.9, 10.9), 3.66 (1H, dd, *J*=16.9, 4.8), 4.38-4.43 (1H, m), 4.45 (1H, ddd, *J*=12.1, 3.0, 1.8), 4.58 (1H, ddd, *J*=12.1, 4.8, 1.8), 7.10-7.30 (4H, m); MS: *m/z* 250 (M^+). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; Cl, 14.14; N, 11.17. Found: C, 57.58; H, 4.47; Cl, 14.21; N, 11.20.

9b (0.18 g, 5% yield) m.p. 190°C (from diisopropylether); IR: 3410, 1720 (cm^{-1}); ^{1}H-NMR: δ 1.50-2.20 (8H, m), 2.80 (1H, br s), 2.92 (1H, dd, *J*=17.8, 5.1), 3.25 (1H, dd, *J*=17.8, 12.1), 3.60-3.70 (1H, m), 4.27 (2H, t, *J*=6.7), 4.51-4.62 (1H, m), 4.96-5.10 (2H, m), 5.75-5.91 (1H, m), 7.07-7.26 (4H, m); after treatment with D_2O: 2.80 (disappears), 3.65 (2H, t, *J*=6.5); MS: *m/z* 350 (M^+). Anal. Calcd for $C_{18}H_{23}ClN_2O_3$: C, 61.62; H, 6.61; Cl, 10.11; N, 7.98. Found: C, 61.70; H, 6.66; Cl, 10.20; N, 8.06.

9d (0.39 g, 8% yield) m.p. 162°C (from methanol); IR: 3400, 1730 (cm^{-1}); ^{1}H-NMR: δ 1.20-2.00 (28H, m), 2.25 (1H, br s), 2.93 (1H, dd, *J*=17.6, 5.2), 3.25 (1H, dd, *J*=17.6, 12.0), 3.60-3.80 (1H, m), 4.25 (2H, t, *J*=6.6), 4.40-4.60 (1H, m), 4.92-5.16 (2H, m), 5.70-5.90 (1H, m), 7.00-7.25 (4H, m); after treatment with D_2O: 2.25 (disappears), 3.70 (2H, t, *J*=6.7); MS: *m/z* 490 (M^+). Anal. Calcd for $C_{28}H_{43}ClN_2O_3$: C, 68.48; H, 8.83; Cl, 7.22; N, 5.70. Found: C, 68.57; H, 8.78; Cl, 7.29; N, 5.63.

9e (0.52 g, 10% yield) m.p. 158°C (from methanol); IR: 3380, 1730 (cm^{-1}); ^{1}H-NMR: δ 1.20-1.80 (32H, m), 2.40 (1H, br s), 2.90 (1H, dd, *J*=17.7, 5.2), 3.27 (1H, dd, *J*=17.7, 12.1), 3.60-3.76 (1H, m), 4.25 (2H, t, *J*=6.9), 4.45-4.58 (1H, m), 4.90-5.05 (2H, m), 5.73-5.87 (1H, m), 7.07-7.25 (4H, m); after treatment with D_2O: 2.40 (disappears), 3.67 (2H, t, *J*=6.8); MS: *m/z* 518 (M^+). Anal. Calcd for $C_{30}H_{47}ClN_2O_3$: C, 69.41; H, 9.12; Cl, 6.83; N, 5.40. Found: C, 69.49; H, 9.06; Cl, 6.89; N, 5.49.

10a (0.50 g, 20% yield) m.p. 230°C, with dec. (from hexane-diisopropylether); IR: 1730 (cm^{-1}); ^{1}H-NMR: δ 2.18-2.44 (4H, m), 3.12 (2H, dd, *J*=17.6, 5.0), 3.48 (2H, dd, *J*=17.6, 12.6), 3.94 (2H, ddd, *J*=12.5, 10.1, 5.0), 4.51 (2H, ddd, *J*=12.5, 8.8, 3.2), 4.76-4.87 (2H, m), 7.10-7.30 (8H, m); MS: *m/z* 500 (M^+). Anal. Calcd for $C_{24}H_{22}Cl_2N_4O_4$: C, 57.50; H, 4.42; Cl, 14.14; N, 11.17. Found: C, 57.44; H, 4.49; Cl, 14.08; N, 11.11.

10b, Racemic form (0.05 g, 2% yield) m.p. 217°C, (from diisopropylether); IR: 1730, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.50-2.00 (8H, m), 2.96 (2H, dd, *J*=17.2, 2.8), 3.23 (2H, dd, *J*=17.2, 10.8), 3.60-3.70 (2H, m), 4.38-4.44 (2H, m), 4.96-5.04 (2H, m), 7.10-7.30 (8H, m); after irradiation at 3.65 δ: 5.01 (2H, dd, *J*=5.8, 3.5); after irradiation at 5.01 δ: 3.65 (2H, dd, *J*=9.5, 2.6); MS: *m/z* 528 (M^+). Anal. Calcd for $C_{26}H_{26}Cl_2N_4O_4$: C, 58.99; H, 4.95; Cl, 13.39; N, 10.58. Found: C, 59.07; H, 5.03; Cl, 13.45; N, 10.64.

10b, Mesoform (0.15 g, 6% yield) m.p. 206°C, (from diisopropylether); IR: 1720, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.50-2.10 (8H, m), 2.82 (2H, dd, *J*=17.1, 2.6), 3.19 (2H, dd, *J*=17.1, 10.8), 3.64-3.72 (2H, m), 4.40-4.50 (2H, m), 5.00-5.06 (2H, m), 7.10-7.30 (8H, m); after irradiation at 3.68 δ: 5.03 (2H, dd, *J*=6.0, 3.1); MS: *m/z* 528 (M^-). Anal. Calcd for $C_{26}H_{26}Cl_2N_4O_4$: C, 58.99; H, 4.95; Cl, 13.39; N, 10.58. Found: C, 59.04; H, 5.04; Cl, 13.33; N, 10.55.

10c, Racemic form (0.56 g, 20% yield) m.p. 230°C, (from hexane-benzene); IR: 1720, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.20-1.60 (12H, m), 2.92 (2H, dd, *J*=17.9, 3.8), 3.31 (2H, dd, *J*=17.9, 12.3), 4.10-4.35 (2H, m), 4.70-4.80 (2H, m), 7.10-7.30 (8H, m); MS: *m/z* 556 (M^+). Anal. Calcd for $C_{28}H_{30}Cl_2N_4O_4$: C, 60.33; H, 5.42; Cl, 12.72; N, 10.05. Found: C, 60.26; H, 5.37; Cl, 12.66; N, 9.96.

10c, Mesoform (0.56 g, 20% yield) m.p. 220°C, (from hexane-benzene); IR: 1730, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.20-1.90 (12H, m), 2.85 (2H, dd, *J*=18.4, 4.2), 3.50 (2H, dd, *J*=18.4, 12.7), 4.00-4.45 (4H, m), 4.65-4.75 (2H, m), 7.10-7.30 (8H, m); MS: *m/z* 556 (M^+). Anal. Calcd for $C_{28}H_{30}Cl_2N_4O_4$: C, 60.33; H, 5.42; Cl, 12.72; N, 10.05. Found: C, 60.39; H, 5.44; Cl, 12.77; N, 10.12.

10d (1.00 g, 30% yield) m.p. 187°C, (from diisopropylether); IR: 1720, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.20-1.80 (28H, m), 2.90 (2H, dd, *J*=18.0, 4.7), 3.28 (2H, dd, *J*=18.0, 11.3), 4.25 (4H, t, *J*=7.0), 4.50-4.60 (2H, m), 7.05-7.30 (8H, m); MS: *m/z* 668 (M^+). Anal. Calcd for $C_{36}H_{46}Cl_2N_4O_4$: C, 64.57; H, 6.92; Cl, 10.59; N, 8.37. Found: C, 64.63; H, 7.00; Cl, 10.66; N, 8.44.

10e (1.04 g, 30% yield) m.p. 187°C, (from diisopropylether); IR: 1720, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.20-1.70 (32H, m), 2.89 (2H, dd, *J*=17.8, 5.0), 3.26 (2H, dd, *J*=17.8, 12.2), 4.20-4.32 (4H, m), 4.40-4.52 (2H, m), 7.00-7.25 (8H, m); after irradiation at 1.70 δ: 4.23 (2H, d, *J*=11.3), 4.28 (2H, d, *J*=11.3); MS: *m/z* 696 (M^+). Anal. Calcd for $C_{38}H_{50}Cl_2N_4O_4$: C, 65.41; H, 7.22; Cl, 10.16; N, 8.03. Found: C, 65.48; H, 7.20; Cl, 10.26; N, 8.11.

16 (0.58 g, 18% yield) m.p. 223°C, (from diisopropylether-methanol); IR: 1715 (cm^{-1}); ^{1}H-NMR: δ 3.40-4.08 (10H, m), 3.70 (1H, dd, *J*=15.3, 11.0), 3.78 (2H, dd, *J*=11.0, 5.6), 4.8-4.94 (1H, m), 7.00-7.25 (4H, m); after irradiation at 3.75 δ: 4.91 (1H, dd, *J*=11.3, 2.8); MS: *m/z* 324 (M^-). Anal. Calcd for $C_{15}H_{17}ClN_2O_4$: C, 55.48; H, 5.28; Cl, 10.92; N, 8.63. Found: C, 55.56; H, 5.20; Cl, 11.01; N, 8.71.

18a, Racemic form (0.34 g, 12% yield) m.p. 312°C, (from methanol); IR: 1720 (cm^{-1}); ^{1}H-NMR: δ 3.28 (4H, d, *J*=8.8), 3.58 (2H, dd, *J*=9.5, 5.4), 3.62-3.65 (4H, m), 3.66 (2H, dd, *J*=9.5, 2.9), 4.23 (2H, dt, *J*=12.6, 3.6), 4.45 (2H, dt, *J*=12.6, 5.0), 4.64-4.75 (2H, m), 7.10-7.28 (8H, m); MS: *m/z* 560 (M^-). Anal. Calcd for $C_{26}H_{26}Cl_2N_4O_6$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98. Found: C, 55.58; H, 4.72; Cl, 12.71; N, 10.06.

18a, Mesoform (0.34 g, 12% yield) m.p. 301°C, (from methanol); IR: 1730 (cm^{-1}); ^{1}H-NMR: δ 3.27 (4H, d, *J*=9.0), 3.45 (2H, dd, *J*=10.0, 6.0), 3.50 (2H, dd, *J*=10.0, 2.5), 3.60-4.50 (8H, m), 4.68-4.76 (2H, m), 7.10-7.30 (8H, m); MS: *m/z* 560 (M^+). Anal. Calcd for $C_{26}H_{26}Cl_2N_4O_6$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98. Found: C, 55.50; H, 4.59; Cl, 12.54; N, 9.88.

18b (0.82 g, 25% yield) m.p. 210°C, (from diisopropylether-methanol); IR: 1710 (cm^{-1}); ^{1}H-NMR: δ 3.44 (2H, dd, *J*=18.4, 13.5), 3.58 (2H, dd, *J*=18.4, 8.0), 4.02 (2H, dd, *J*=10.0, 1.8), 4.57 (2H, dd, *J*=10.0, 2.0),

4.92-5.00 (2H, m), 6.90-7.30 (8H, m); after irradiation at 3.51 δ: 4.96 (1H, t, *J*=2.0, 1.8); MS: *m/z* 656 (M^+). Anal. Calcd for $C_{34}H_{26}Cl_2N_4O_6$: C, 62.11; H, 3.99; Cl, 10.78; N, 8.52. Found: C, 62.04; H, 4.02; Cl, 10.71; N, 8.60.

18c (0.32 g, 10% yield); IR: 1730, 1715 (cm^{-1}); ^{1}H-NMR: δ 3.15-3.33 (10H, m), 3.50-3.77 (16H, m), 4.25-4.47 (4H, m), 4.60-4.71 (2H, m), 7.10-7.30 (8H, m); MS: *m/z* 648 (M^+). Anal. Calcd for $C_{30}H_{34}Cl_2N_4O_8$: C, 55.48; H, 5.28; Cl, 10.92; N, 8.63. Found: C, 55.39; H, 5.21; Cl, 10.79; N, 8.59.

General procedure for the isolation of hydrazonyl chlorides 8a-e and 17c. A solution of the hydrazonyl chlorides **4** or **14c** (1 mmol) in dry dioxane (50 mL) was added with silver carbonate (0.55 g, 2 mmol), and stirred in the dark at room temperature for 24 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with light petroleum/ethyl acetate 2:1. Products **8** were obtained as thick oils not analytically pure, while **17c** was a solid material which was recrystallised. Considerable amounts of the starting hydrazonyl chloride (46 to 59%) was recovered.

8a (14 mg, 5% yield); IR: 3260, 1730, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.85-2.54 (4H, m), 3.24 (1H, dd, *J*=17.6, 10.6), 3.42 (1H, dd, *J*=10.6, 5.9), 4.27 (4H, t, *J*=7.0), 4.10-4.35 (1H, m), 4.90-5.20 (2H, m), 5.60-6.10 (1H, m), 7.00-7.60 (8H, m), 8.40 (1H, br s); MS: *m/z* 536 (M^+).

8b (20 mg, 7% yield); IR: 3250, 1730, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.65-2.35 (8H, m), 3.23 (1H, dd, *J*=17.6, 11.8), 3.36 (1H, dd, *J*=17.6, 5.9), 4.25 (4H, t, *J*=6.8), 4.10-4.30 (1H, m), 4.88-5.20 (2H, m), 5.55-6.10 (1H, m), 7.00-7.49 (8H, m), 8.38 (1H, br s); MS: *m/z* 564 (M^+).

8c (18 mg, 6% yield); IR: 3270, 1720, 1705 (cm^{-1}); ^{1}H-NMR: δ 1.15-2.40 (12H, m), 3.20 (1H, dd, *J*=17.8, 11.8), 3.39 (1H, dd, *J*=17.8, 5.9), 4.28 (4H, t, *J*=6.2), 4.05-4.40 (1H, m), 4.75-5.15 (2H, m), 5.50-6.10 (1H, m), 6.95-7.50 (8H, m), 8.35 (1H, br s); MS: *m/z* 592 (M^+).

8d (18 mg, 5% yield); IR: 3270, 1730, 1710 (cm^{-1}); ^{1}H-NMR: δ 1.20-2.20 (28H, m), 2.95 (1H, dd, *J*=22.5, 7.5), 3.30 (1H, dd, *J*=15.0, 7.5), 4.30 (4H, t, *J*=6.5), 4.10-4.40 (1H, m), 4.80-5.12 (2H, m), 5.52-6.08 (1H, m), 7.00-7.38 (8H, m), 8.38 (1H, br s); MS: *m/z* 704 (M^+).

8e (20 mg, 5% yield); IR: 3270, 1720, 1705 (cm^{-1}); ^{1}H-NMR: δ 1.10-2.40 (32H, m), 2.90 (1H, dd, *J*=17.6, 11.8), 3.28 (1H, dd, *J*=17.6, 5.9), 4.25 (4H, t, *J*=6.9), 4.05-4.40 (1H, m), 4.75-5.15 (2H, m), 5.50-6.10 (1H, m), 6.95-7.50 (8H, m), 8.35 (1H, br s); MS: *m/z* 732 (M^+).

17c (48 mg, 14% yield) m.p. 116°C (from diisopropylether); IR: 3240, 1735, 1710 (cm^{-1}); ^{1}H-NMR: δ 3.11 (1H, dd, *J*=18.0, 5.4), 3.26 (1H, dd, *J*=18.0, 12.0), 3.46-4.45 (20H, m), 4.58-4.67 (1H, m), 5.12-5.28 (2H, m), 5.82-5.96 (1H, m), 7.10-7.30 (8H, m), 8.42 (1H, br s); MS: *m/z* 684 (M^+). Anal. Calcd for $C_{30}H_{35}Cl_3N_4O_8$: C, 52.53; H, 5.14; Cl, 15.50; N, 8.17. Found: C, 52.60; H, 5.17; Cl, 15.60; N, 8.25.

General procedure for the reaction of compounds 8a-e and 17c with silver carbonate in dioxane. A solution of **8a-e** or **17c** (1 mmol) in dry dioxane (50 mL) was added with silver carbonate (0.55 g, 2 mmol), and stirred in the dark at room temperature for 96 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with light petroleum/ethyl acetate

1:1. After crystallisation from diisopropylether, dimeric products **10** and **18c** were obtained as mixtures of diastereoisomers with the following yields: **10a**, 44%; **10b**, 38%; **10c**, 45%; **10d**, 56%; **10e**, 44%; **18c**, 42%.

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