Selective Synthesis of Dihalo-Substituted Unsaturated Carboxylic Acids and Derivatives

Sandrine Langle,^a Samuel Inack Ngi,^b Elsa Anselmi,^b Mohamed Abarbri,^b Jérôme Thibonnet,^b Alain Duchêne*^b

- ^a Laboratoire Groupe SUCRES, Unité Mixte 7565 CNRS, Université Henri Poincaré-Nancy 1, B.P. 239, 54506 Nancy-Vandoeuvre, France
- ^b Laboratoire de Synthèse et Physicochimie Organique et Thérapeutique, Faculté des Sciences et Techniques de Tours, Parc de Granmont, 37200 Tours, France
- Fax +33(2)47367073; E-mail: alain.duchene@univ-tours.fr

Received 22 December 2006

Abstract: A selective one-pot procedure was developed for the production of *E*-dihalo-substituted α,β -unsaturated alkenoic acids and derivatives from the corresponding α,β -unsaturated alkynoic acids.

Key words: α , β -unsaturated acids, carboxylic acids, α , β -dihalosubstituted acrylic acids, halogenation, addition reactions

Functionalized 1,2-dihaloalk-1-enes are useful intermediates in substitution reactions and in direct coupling reactions for forming new carbon–carbon bonds involving organolithium, organocopper, organozinc, organotin, or palladium cross-coupling reactions. 1,2-Diiodoalkenes can be prepared by a variety of methods, such as aluminaor Florisil-assisted iodination of alkynes,¹ direct addition of iodine (or bromine) to alkynes,² and the use of electropositive iodonium (or bromonium) species in the presence of iodonium ions.³ Iodine monochloride or monobromide is usually used as an intermediate to produce iodoalkene, as, for example, in the classical methodology for the transformation of vinylsilane into vinyl iodide or to synthesize unsymmetrical 2,3-dihaloalk-2-en-1-ols or 2,3-dihaloalk-2-enoates.⁴

We recently demonstrated the use of iodovinylic acids as a flexible method for the stereoselective synthesis of polyenes containing natural products such as retinoic and retinoid acids. In view of the surprising scarcity of literature reports on the synthesis of dihaloalkenoic acids,⁵ we report here the efficient synthesis of (*E*)- or (*Z*)-dihaloalkenoic acids or derivatives.

We first studied the effects of the reaction conditions on the selectivity in the addition of iodine monochloride or -bromide to propiolic and tetrolic acid in diethyl ether (Scheme 1, Table 1).



Scheme 1 Synthesis of 2,3-dihaloalk-2-enoic acids

The best results in terms of selectivity were obtained at 0 °C for the addition of iodine monochloride or -bromide to propiolic acid (Table 1, entries 1 and 3), and at 35 °C for the addition of iodine monochloride or -bromide to tetrolic acid (Table 1, entries 2 and 4). We also tried to isomerize acids 1–4 into the corresponding *Z*-acids by heating, addition of iodine, or irradiation with a UV lamp; only the irradiation method resulted in the following interesting isomerization results: 1 (*Z*/*E*, 82:18, after 12 h), 2 (*Z*/*E*, 49:51, after 10 h), 3 (*Z*/*E*, 90:10, after 14 h; pure *Z*-acid obtained by crystallization), and 4 (*Z*/*E*, 30:70, after 8 h).

The application of these reactions was extended to other alk-2-ynoic acids and derivatives (Scheme 2, Table 2).



Scheme 2 Synthesis of 2,3-dihaloalk-2-enoic acids and derivatives

In all cases, under the various conditions shown in Table 2, these additions were regio- and stereoselective, resulting from *trans* addition at the triple bond of the starting alk-2-ynoic acid, and the E/Z ratio was always in favor of the *E*-isomer. In the case of unsymmetrical dihalogens, the iodine atom was always in the α -position relative to the carbonyl group. It should be noted that stannyl esters and amides (Table 2, entries 5, 10, and 11) provided the same selectivity. Some stereoisomerically pure *E*-isomers were obtained by crystallization, but this resulted in decreased yield. Interestingly, in all cases no cyclization product leading to a four-membered-ring product was obtained.

To confirm the *E*-structure of some 2,3-dihaloalk-2-enoic acids, X-ray analysis was performed on compounds **6** (Figure 1), **10** (Figure 2), **11**, and **16**.

In conclusion, we report here a new synthetic method for the synthesis of symmetrical and unsymmetrical α,β -dihaloacrylic acids and derivatives. The reactivity of these new compounds is currently under investigation in our laboratory.

SYNTHESIS 2007, No. 11, pp 1724–1728 Advanced online publication: 02.05.2007 DOI: 10.1055/s-2007-966043; Art ID: Z27106SS © Georg Thieme Verlag Stuttgart · New York

Entry	R	IX	Temp (°C)	Time (h)	Product	E/Z ratio	Yield (%)
1	Н	ICl	0	12	CI CO ₂ H	98:2 ^{b,c}	55
2	Ме	ICI	35	12	1 CI CO ₂ H 2	97:3	48
3	Н	IBr	0	18	Br CO ₂ H	>99:1	62
4	Me	IBr	35	14	Br CO ₂ H	98:2 ^b	50

Table 1 Addition of Iodine Monochloride or Iodine Monobromide to Propiolic or Tetrolic Acida

^a See Scheme 1 for corresponding reaction.

^b The crude product was contaminated with the corresponding dichloro or diiodo acid.⁶

^c Compound **1** must be used as soon as possible and kept away from light.



Figure 1 ORTEP drawing and labeling scheme for **6** (ellipsoids are set at 50% probability)

All reactions were carried out under an inert atmosphere (argon or N₂). Flash chromatography was performed on silica gel (Merck, 230–400 mesh). ¹H (200 MHz) and ¹³C (50.3 MHz) NMR spectra were recorded on a Bruker AC 200 NMR spectrometer; CDCl₃ was used as solvent, and the chemical shifts δ are reported relative to CDCl₃ (δ_H = 7.25, δ_C = 77.0). Mass spectra were obtained on a Hewlett Packard (engine 5989A) in the GC/MS (70 eV) mode or direct injection mode. IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrophotometer.

(E)-3-Chloro-2-iodobut-2-enoic Acid (2); Typical Procedure

A 100-mL, three-necked, round-bottomed flask protected from light, equipped with a magnetic stirrer, reflux condenser fitted with an argon inlet adapter, thermometer, and pressure-equalizing dropping funnel, was charged with tetrolic acid (5 g, 0.06 mol) and Et₂O (15 mL). The mixture was cooled with an ice–salt bath to -5 °C, and maintained under an argon atmosphere. A soln of ICl (12.2 g, 0.075

Figure 2 ORTEP drawing and labeling scheme for 10 (ellipsoids are set at 50% probability)

mol) in Et₂O (25 mL) was added dropwise over 10 min while the reaction mixture was vigorously stirred. After the addition, the resulting soln was stirred for an additional 15 h while being cooled in the ice bath. The reaction mixture was quenched by dropwise addition of aq sat. NaHSO₃ soln (30 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (4×25 mL). The combined organic layers were washed with aq sat. NaCl soln (25 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure; this gave **2** as colorless crystals. The crude product was recrystallized from a minimum amount of CH₂Cl₂; this yielded pure **2**.

Yield: 7.03 g (48%); mp 73-75 °C.

IR (KBr): 3100–2600, 3087, 1698, 1592, 1273 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ (*E*-isomer) = 2.54 (s, 3 H), 11.60 (br s, 1 H); δ (*Z*-isomer, 3%) = 2.78 (s, 3 H).

¹³C NMR (50 MHz, CDCl₃): δ = 31.4, 80.9, 138.8, 170.5.

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Table 2 Addition of Dihalogens to Alk-2-ynoic Acids^a

Entry	\mathbf{R}^1	\mathbb{R}^2	X–X′	Temp (°C)	Time (h)	Solvent	Product	E/Z ratio	Yield ^b (%)
1	Me	ОН	Br ₂	-5	0.2	МеОН	Br Br Br	>99:1	80
2	CH ₂ OMe	ОН	Br ₂	-5	0.5	none	Br CO ₂ H MeO Br	>99:1	87
3	<i>n</i> -C ₅ H ₁₁	ОН	Br ₂	-5	4	CHCl ₃	Br CO ₂ H n-C ₅ H ₁₁ Br	91:9	97
4	Н	ОН	I ₂	35	12	Et ₂ O	$\begin{array}{c} 7 \\ I \\ H \\ H \end{array} \xrightarrow{CO_2H} \\ I \\ $	>99:1	68
5	Me	NHBz	I ₂	35	12	Et ₂ O		>99:1	70
6	Me	ОН	I ₂	35	18	Et ₂ O		>99:1	85
7	CH ₂ OMe	ОН	I ₂	35	18	Et ₂ O		>99:1	84
8	<i>n</i> -C ₅ H ₁₁	ОН	I ₂	25	12	Et ₂ O	$ \begin{array}{c} I \\ $	>99:1	95
9	Ph	ОН	I ₂	35	18	Et ₂ O	$PH \qquad I \qquad $	>99:1	80
10	Н	OSnBu ₃	ICI	0	12	Et ₂ O	$\begin{array}{c} \text{CO}_2\text{SnBu}_3\\ \text{H} & \text{I} \end{array}$	98:2	55
11	Me	OSnBu ₃	ICI	35	12	Et ₂ O	CI CI CO ₂ SnBu ₃	98:2	50
12	CH ₂ OMe	ОН	ICl	-5	12	Et ₂ O		87:13	47 (88°)

^a See Scheme 2 for corresponding reaction.

^b Isolated yield after crystallization.

^c Yield estimated by NMR.

MS (EI, 70 eV): *m*/*z* (%) = 248 (18) [M + 2], 246 (55) [M⁺], 211 (31), 210 (48), 127 (24), 84 (12), 83 (39), 73 (15), 67 (26), 55 (26), 49 (18), 45 (20), 39 (100), 38 (37), 37 (24).

Anal. Calcd for $C_4H_4CIIO_2$: C, 19.50; H, 1.64. Found: C, 19.49; H, 1.69.

(*E*)-**3-Chloro-2-iodoprop-2-enoic** Acid (1) Mp 67–69 °C.

IR (KBr): 3250-2600, 3047, 1685, 1600, 1257 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ (*E*-isomer) = 7.28 (s, 1 H), 11.40 (br s, 1 H); δ (*Z*-isomer, 2%) = 8.11 (s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 84.8, 133.6, 168.4.

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$$\begin{split} \text{MS} & (\text{EI}, 70 \text{ eV}): \textit{m/z} \, (\%) = 234 \, (6) \, [\text{M}+2], 232 \, (23) \, [\text{M}^+], 197 \, (15), \\ 152 \, (10), 127 \, (36), 107 \, (10), 105 \, (20), 61 \, (19), 60 \, (11), 53 \, (24), 50 \\ (17), 45 \, (22), 44 \, (100), 42 \, (11). \end{split}$$

¹³C NMR: 91.6, 133.0, 169.3.

Anal. Calcd for $C_3H_2CIIO_2$: C, 15.50; H, 0.87. Found: C, 15.62; H, 0.95.

(*E*)-**3-Bromo-2-iodoprop-2-enoic** Acid (3) Mp 63–65 °C.

IR (KBr): 3200–2600, 3063, 1691, 1624, 1215 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ (*E*-isomer) = 7.49 (s, 1 H), 11.66 (br s, 1 H); δ (*Z*-isomer, 1%) = 8.61 (s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 84.1, 118.6, 168.3.

MS (EI, 70 eV): m/z (%) = 234 (1) [M – 44], 232 (1) [M – 44], 152 (100), 127 (32), 44 (56).

Anal. Calcd for $C_3H_2BrIO_2$: C, 13.01; H, 0.73. Found: C, 12.89; H, 0.79.

(*E*)-3-Bromo-2-iodobut-2-enoic Acid (4) Mp 102–104 $^{\circ}$ C.

IR (KBr): 3200–2600, 3074, 1680, 1623, 1282 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ (*E*-isomer) = 2.66 (s, 3 H), 11.3 (br s, 1 H); δ (*Z*-isomer, 2%) = 2.87 (s, 3 H).

¹³C NMR (50 MHz, CDCl₃): δ = 34.0, 81.2, 125.9, 171.2.

MS (EI, 70 eV): m/z (%) = 292 (20) [M⁺], 290 (20), 211 (81), 127 (11), 84 (13), 83 (14), 67 (23), 55 (23), 45 (13), 43 (10), 39 (100), 38 (29), 37 (16).

Anal. Calcd for $C_4H_4BrIO_2$: C, 16.52; H, 1.39. Found: C, 16.63; H, 1.46.

(E)-2,3-Dibromobut-2-enoic Acid (5)

Mp 81–83 °C.

IR (KBr) : 3400–2300, 1690, 1599, 1273 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 2.58 (s, 3 H), 11.32 (br s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 37.0, 116.8, 125.2, 169.2.

MS (EI, 70 eV): m/z (%) = 244 (16) [M⁺], 165 (41), 163 (44), 84 (39), 67 (32), 55 (11), 44 (40), 40 (38), 39 (100), 38 (40), 37 (27).

Anal. Calcd for C₄H₄Br₂O₂: C, 19.70; H, 1.65. Found: C, 19.79; H, 1.69.

(*E*)-2,3-Dibromo-4-methoxybut-2-enoic Acid (6) Mp 66-68 °C.

IR (KBr): 3670–2280, 1723, 1623, 1451, 1258 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 3.43 (s, 3 H), 4.44 (s, 2 H), 9.9 (br s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 58.2, 74.6, 109.6, 125.6, 166.9.

MS (EI, 70 eV): m/z (%) = 274 (8) [M + 2], 195 (63), 193 (61), 163 (100), 161 (95), 53 (10), 45 (47), 39 (32), 38 (22), 37 (11).

Anal. Calcd for $C_5H_6Br_2O_3$: C, 21.92; H, 2.21. Found: C, 21.98; H, 2.33.

(*E*)-2,3-Dibromooct-2-enoic Acid (7)

IR (neat): 3714–2274, 1718, 1628, 1466, 1381, 1259 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): $\delta = 0.92$ (t, J = 7.5 Hz, 3 H), 1.28–1.37 (m, 4 H), 1.61–1.67 (m, 2 H), 2.77 (t, J = 7.5 Hz, 2 H), 10.90 (br s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 13.8, 22.3, 26.6, 30.5, 41.4, 106.1, 130.8, 168.6.

 $\begin{array}{l} \text{MS (EI, 70 eV): } \textit{m/z (\%) = 300 (4) [M + 2], 220 (14), 219 (14), 179 \\ (14), 177 (16), 165 (11), 163 (13), 139 (15), 121 (13), 111 (17), 97 \\ (13), 95 (25), 94 (10), 93 (68), 81 (30), 79 (16), 67 (28), 66 (12), 65 \\ (10), 57 (22), 56 (13), 55 (45), 53 (18), 51 (15), 44 (16), 43 (37), 42 \\ (10), 41 (100), 39 (55), 38 (12). \end{array}$

Anal. Calcd for $C_8H_{12}Br_2O_2$: C, 32.03; H, 4.03. Found: C, 32.14; H, 4.13.

(*E*)-2,3-Diiodoprop-2-enoic Acid (8)^{2a} Mp 104–106 °C.

IR (KBr): 3100–2600, 3054, 1701, 1545 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 8.09 (s, 1 H), 11.70 (br s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 85.9, 91.9, 169.3.

MS (EI, 70 eV): m/z (%) = 324 (73) [M⁺], 254, 36), 197 (71), 153 (28), 152 (22), 127 (88), 69 (28), 53 (100).

Anal. Calcd for $C_3H_2I_2O_2$: C, 11.13; H, 0.62. Found: C, 11.22; H, 0.66.

(*E*)-*N*-Benzyl-2,3-diiodobut-2-enamide (9) Mp 104–105 °C.

IR (KBr): 3418, 3053, 1654 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 2.65 (s, 3 H), 4.53 (s, 1 H), 4.56 (s, 1 H), 5.85 (br s, 1 H), 7.33–7.40 (m, 5 H).

¹³C NMR (50 MHz, CDCl₃): δ = 38.7, 44.5, 89.3, 96.2, 128.2, 128.6, 129.2, 137.6, 168.2 (C₁).

 $\begin{array}{l} \text{MS (EI, 70 eV): } \textit{m/z (\%)} = 428 \ (4) \ [\text{M}+1], \ 300 \ (61), \ 254 \ (43), \ 174 \ (17), \ 173 \ (99), \ 172 \ (23), \ 144 \ (11), \ 130 \ (34), \ 129 \ (27), \ 127 \ (32), \ 115 \ (14), \ 106 \ (37), \ 104 \ (13), \ 91 \ (100), \ 19 \ (19), \ 77 \ (26), \ 67 \ (66), \ 65 \ (27), \ 51 \ (23), \ 39 \ (64), \ 38 \ (16). \end{array}$

Anal. Calcd for $C_{11}H_{11}I_2NO:$ C, 30.94; H, 2.60; N, 3.28. Found: C, 31.06; H, 2.70; N, 3.35.

(*E*)-2,3-Diiodobut-2-enoic Acid (10)

Mp 113–115 °C.

IR (KBr): 3300–2700, 1719, 1625, 1445, 1384, 1235 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 2.75 (s, 3 H), 9.50 (br s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 40.2, 84.6, 100.2, 171.6.

MS (EI, 70 eV): m/z (%) = 338 (22) [M⁺], 254 (39), 211 (61), 127 (34), 84 (19), 67 (40), 55 (19), 40 (12), 39 (100), 38 (30), 37 (18). Anal. Calcd for C₄H₄I₂O₂: C, 14.22; H, 1.19. Found: C, 14.15; H, 1.24.

(E)-2,3-Diiodo-4-methoxybut-2-enoic Acid (11)

Mp 84–86 °C.

IR (KBr): 3684–2303, 1715, 1445, 1360, 1230 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 3.41 (s, 3 H), 4.28 (s, 2 H), 10.30 (s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 57.9, 81.4, 84.4, 103.8, 169.9.

MS (EI, 70 eV): m/z (%) = 368 (1) [M⁺], 254 (100), 127 (14), 39 (11).

Anal. Calcd for $C_5H_6I_2O_3$: C, 16.32; H, 1.64. Found: C, 16.45; H, 1.60.

(E)-2,3-Diiodooct-2-enoic Acid (12)

IR (neat): 3692–2397, 1703, 1606, 1455, 1383, 1255 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 0.91 (t, *J* = 7.5 Hz, 3 H), 1.30–1.37 (m, 4 H), 1.54–1.60 (m, 2 H), 2.75 (t, *J* = 7.4 Hz, 2 H), 10.60 (br s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 13.9, 22.3, 27.5, 30.2, 49.2, 82.7, 107.4, 171.0.

MS (EI, 70 eV): m/z (%) = 394 (0.1) [M⁺], 254 (100), 127 (29), 95 (12), 67 (17), 55 (22), 51 (12), 49 (22), 43 (14), 41 (41), 39 (29), 35 (13).

Anal. Calcd for $C_8H_{12}I_2O_2$: C, 24.39; H, 3.07. Found: C, 24.32; H, 3.14.

(*E*)-2,3-Diiodo-3-phenylprop-2-enoic Acid (13) Mp 173–175 °C.

IR (KBr): 3300–2600, 3055, 1720, 1660, 1603, 1586, 1485, 1391, 1220 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 7.28–7.46 (m, 5 H), 11.30 (br s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 85.6, 99.7, 128.1 (2 C), 129.0 (2 C), 129.6, 145.8, 169.7.

Anal. Calcd for $C_9H_6I_2O_2$: C, 27.03; H, 1.51. Found: C, 26.91; H, 1.58.

Tributylstannyl (*E*)-**3-Chloro-2-iodoprop-2-enoate** (14) Mp 58–60 °C.

IR (KBr): 2956, 2921, 2854, 1611, 1586, 1461 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ (*E*-isomer) = 0.94 (t, J = 7.1 Hz, 9 H), 1.15–1.55 (m, 12 H), 1.6–1.9 (m, 6 H), 6.87 (s, 1 H); δ (*Z*-isomer, 2%) = 7.83 (s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 14.2, 17.6 (3 C, ${}^{1}J_{\text{Sn-C}}$ = 332–349 Hz), 27.6 (3 C, ${}^{3}J_{\text{Sn-C}}$ = 62 Hz), 28.3 (3 C, ${}^{2}J_{\text{Sn-C}}$ = 21 Hz), 89.6, 126, 167.7.

MS (EI, 70 eV): m/z (%) = 465 (80) [M – 57], 359 (47), 305 (38), 269 (45), 247 (33), 177 (27), 153 (14), 127 (17), 121 (24), 119 (19), 105 (15), 57 (67), 53 (32), 45 (10), 41 (100), 39 (28).

Tributylstannyl (E)-3-Chloro-2-iodobut-2-enoate (15) Mp 80–82 °C.

IR (KBr): 2956, 2922, 2861, 2854, 1602, 1545, 1469 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 0.95 (t, J = 7.1 Hz, 9 H), 1.2–1.85 (m, 18 H), 2.46 (s, 3 H).

¹³C NMR (50 MHz, CDCl₃): δ = 14.2 (3 C), 17.5 (3 C, ¹ J_{Sn-C} = 333–349 Hz), 27.6 (3 C, ³ J_{Sn-C} = 62 Hz), 28.2 (3 C, ² J_{Sn-C} = 22 Hz), 30.1, 85.2, 132.1, 170.

(*E*)-3-Chloro-2-iodo-4-methoxybut-2-enoic Acid (16) Mp 60–62 °C.

IR (KBr): 3681–2370, 1716, 1450, 1359, 1255 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ = 3.44 (s, 3 H), 4.44 (s, 2 H), 11.1 (s, 1 H).

¹³C NMR (50 MHz, CDCl₃): δ = 58.2, 76.6, 82.4, 135.8, 168.6.

MS (EI, 70 eV): m/z (%) = 278 (4) [M + 2], 276 (15) [M⁺], 241 (51), 209 (62), 128 (13), 127 (24), 117 (20), 113 (30), 84 (21), 73 (10), 69 (44), 66 (10), 61 (14), 55 (25), 53 (21), 45 (98), 44 (57), 42 (17), 41 (40), 40 (18), 39 (100), 38 (49), 37 (23), 36 (26).

Anal. Calcd for $C_5H_6CIIO_3$: C, 21.72; H, 2.19. Found: C, 21.78; H, 2.11.

X-ray Crystallography

Suitable single crystals of **6**, **10**, **11**, and **16** were mounted on a glass fiber. Data collection was carried out at r.t. on a Bruker-Nonius Kappa CCD diffractometer equipped with graphite-monochromated Mo(K α) radiation ($\lambda = 0.71073$ Å). Cell parameters were retrieved and refined using DENZO-SMN software⁷ on all

reflections. Data reductions were performed with the DENZO-SMN software.⁸ An empirical absorption correction was applied to each data set based on the symmetry-equivalent reflections using the SORTAV program.⁹ Structures were resolved with either SIR92¹⁰ or SHELXS-97¹¹ and refined with the SHELXL-97 program.¹² The hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC, under nos. 615418 (compound **6**), 615417 (compound **10**), 615415 (compound **11**), and 615419 (compound **16**). Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk or www.http://www.ccdc.cam.ac.uk].

Acknowledgment

We thank MENRT for providing financial support, and the 'Service d'analyse chimique du vivant de Tours' for recording NMR and mass spectra, and the 'Laboratoire de Cristallochimie' of Marseille University for X-ray diffraction analysis.

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