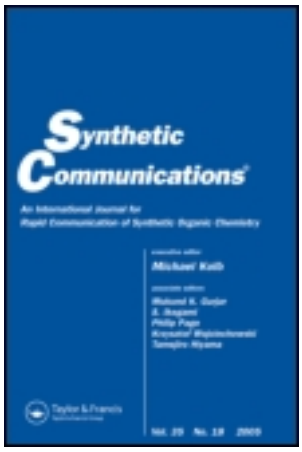

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A Facile Synthesis of (E,Z)-3-Chloro-2-propenamides, Acids, and Esters from 2,3-Acetylenic Acids with Oxalyl Chloride in DMF

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A Facile Synthesis of (*E*,*Z*)-3-Chloro-2-propenamides, Acids, and Esters from 2,3-Acetylenic Acids with Oxalyl Chloride in DMF

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ABSTRACT

A simple route is described for the synthesis of *E* and *Z* 3-chloro-2-propenamides (**4a-e**), esters (**3a**) and acids (**2a-c**) by the reaction of 2,3-acetylenic acids with oxalyl chloride in DMF followed by treatment of the corresponding 3-chloro-2-propenoyl chloride derivative with amines, alcohol and water.

Key Words: 2,3-Acetylenic acids; 3-Chloro-2-alkenoic acids; Hydrochlorination; Oxalyl chloride; DMF.

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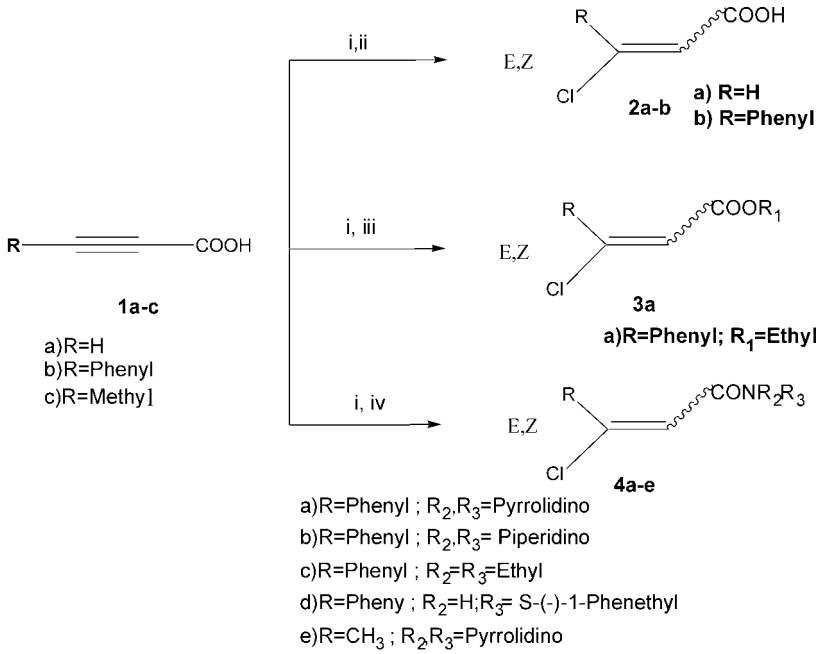
Recently, we have demonstrated that 2,3-acetylenic acids react with thionyl chloride in dimethylformamide to give *E* and *Z* 3-chloro-2-alkenoic acid derivatives.[1] The versatility of this method consists in both the hydrochlorination of the acetylenic bond and the in situ generation of the corresponding 3-chloro-2-propenoyl chloride intermediate, which permits its reaction with solvent nucleophiles as water and alcohols giving acids and esters and it has been extended for the preparation of 3-chloro-2-alkenamides. Due to their high functionality[2–5] (vinylic halogen bond, carbon–carbon double bond and a carboxylic acid, ester or amide), these compounds have proved to be valuable and versatile intermediates in the design and construction of more elaborated and biological active molecules, specially acrylamide derivatives.[6–9]

In continuation of our investigation exploring and extending the use of other potential hydrohalogenating agents and other nucleophiles, we reported herein the results of our studies on the hydrochlorination of 2,3-acetylenic acids with oxalyl chloride in DMF. Thus, the reaction of 2-propynoic acid (**1a**), 3-phenyl-2-propynoic acid (**1b**) and 2-butynoic acid (**1c**) with oxalyl



Scheme 1. Conditions (i) DMF 0°C and ($COCl_2$); (ii) H_2O; (iii) n-pentane and alchol, 6 h r.t., and (iv) −50°C, amine/CH_2Cl_2 6 h r.t.

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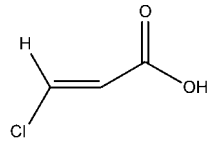
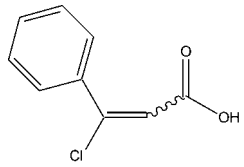
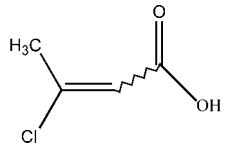
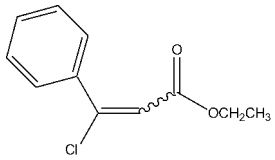
Table 1. *E*,*Z*-3-Chloro-2-alkenoic acids **2a-c** and esters **3a** obtained according to Scheme 1.

Compound	3-Chloro-2-alkenoic acids and esters	Overall yield[a]	*E*,*Z* ratio[b]
2a		75	E[c]
2b		88	25 : 75
2c		80	40 : 60
3a		75	24 : 76

[a]Yield of isolated mixture after work-up.
[b]Calculated based on the NMR spectral data of the purified mixture.
[c]Only *E* isomer was isolated after work-up.

chloride in DMF, afforded the corresponding *E*,*Z*-3-chloro-2-propenoic acids, esters and amides derivatives, when treating the 3-chloro-2-propenoyl chloride intermediate either with water (ice), alcohol or amines (Sch. 1).

A variety of 2,3-acetylenic acids were submitted to these reactions and conditions and the results are summarized in Tables 1 and 2. When the reaction mixture was treated with ice, alcohol (ethanol) or amines (pyrrolidine, piperidine, diethylamine and S (−)-1-phenylethylamine) in dichloromethane at −50°C, the corresponding *E*,*Z*-3-chloro-2-alkenoic acids (**2a-c**) and *E*,*Z*-3-chloro-2-alkenoates (**3a**) (Table 1) and *E*,*Z*-3-chloro-alkenamides (**4a-e**) (Table 2) were formed respectively in moderated to high yield. The formation of a Vielsmeier–Haack type $(COCl)_2$–DMF complex[10] may account for the generation of hydrogen chloride in the hydrochlorination of the triple bond and the formation of the acid chloride intermediate.[11] In the

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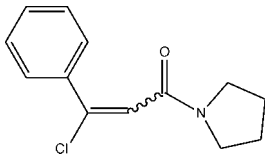
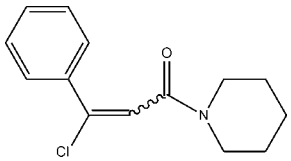
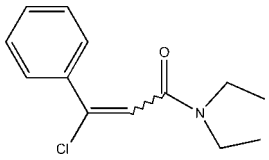
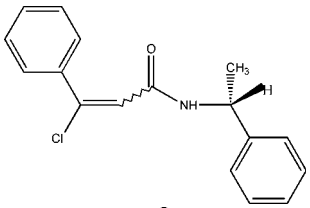
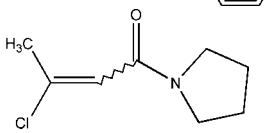
Table 2. *E,Z*-3-Chloro-2-propenamides **4a-e** obtained according to Scheme 1.

Compound	*E,Z*-3-Chloro-2-propenamides	Overall yield[a]	*E,Z* ratio[b]
4a		75	24 : 76
4b		76	10[c] : 90
4c		82	Z[d]
4d		76	Z[d]
4e		70	30[e] : 70

[a]Yield of isolated mixture after work-up.
[b]Calculated based on the NMR spectral data of the purified mixture.
[c]A 7 : 3 *E,Z* mixture by ^{1}H NMR as an oil was separated.
[d]Only *Z* isomer was isolated after work-up.
[e]A 8 : 2 *E,Z* mixture by NMR as an oil was separated.

reaction of **1a**, the predominant product was the *E*-(**2a**) isomer, while the reaction of **1b** and **1c** gave the *Z*-isomers as predominant products.

This new methodology avoids the traditional two steps sequence for the synthesis of 3-alkenoic acid derivatives[12–14] (hydrohalogenation of the previously prepared carbonyl derivative). The described one pot procedure is carry out under more gentle conditions, such as lower temperature, short times

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and easier work-up when compared with other methods[12,13] and our previous report.[1]

In conclusion, we have developed a novel and convenient methodology for the synthesis of 3-chloro-2-alkenoic acid derivatives, via the simple reaction of 2,3-acetylenic acids with oxalyl chloride in DMF under mild conditions and in short reaction times. A more extensive search concerning these results, their mechanistic aspects and some other potential applications are ongoing in our laboratory.

EXPERIMENTAL

IR spectra were recorded on a Excalibur (Biorad) FT-IR. ^{1}H NMR and ^{13}C NMR were recorded on a Eclipse + (JEOL) 400 MHz spectrometer using $CDCl_3$ as solvent. Mass spectra were obtained on a Series II-HP5890 Gas-Chromatograph (Hewlett Packard) with a HP5971A (Hewlett Packard) Mass Detector. The high resolution mass spectra were obtained on a JEOL JMS-AX505WA mass spectrometer. Specific rotation was determined at 20°C at the Hg line (546 nm) on a Perkin-Elmer 341 model polarimeter. Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

General procedure for the preparation of *E*,*Z*-3-chloro-2-alkenoic acids, esters and amides. To a solution of acetylenic acid **1** (2 mmol) in dry DMF (1.5 mL) cooled at 0°C was slowly added oxalyl chloride (4.1 mmol). After stirring for 45 min, the reaction mixture was poured on ice and the resulting aqueous solution was extracted with ethyl ether or dichloromethane. The organic layer was then washed with water, dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to give a mixture of the corresponding alkenoic acids (**2a-c**). For both the esters (**3a**) and amides (**4a-e**), the acid chloride containing reaction mixture was treated in a different way. In the case of esters (**3a**), after stirring for 45 min., *n*-pentane was added (3 mL) and then ethanol (4 mmol) with additional stirring at room temperature for 6 h. For the amides (**4a-e**), 3 mL of dry dichloromethane was added lowering the temperature to −50°C, followed by slow (drop by drop) addition of the corresponding amine (4.0 mmol) dissolved in dry dichloromethane (5 mL) to the reaction mixture with stirring for additional 6 h. The *E*,*Z*-ester and amide mixtures were separated by column chromatography on Silicagel, with n-hexane and ethyl acetate as eluent, (80 : 20) and (75 : 25) respectively. All products **2a**,[12,13] **2b**,[14,15] **2c**,[15,16a,16b] **3a**[17] and **4a**[18] were known except **4b**, **4c**, **4d** and **4e**.

(*E*)-3-Chloropropenoic acid (2a). m.p. 80–81°C (Lit.[12] 82–83°C). ^{1}H NMR ($CDCl_3$): δ 6.26 (d, 1H, $J = 13$ Hz), 7.52 (d, 1H, $J = 13$ Hz), 9.24 (bs, 1H). MS m/z (%): $M^{+\cdot}$ 106 (90), 89 (100), 71 (60), 61 (50), 45 (30).

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(*Z*)-3-Chloro-3-phenyl-2-propenoic acid (2b). m.p. 134–135°C (Lit.[14,15] 133°C). ^{1}H NMR ($CDCl_3$): δ 6.59 (s, 1H), 7.45–7.72 (m, 5H), 10.2 (bs, 1H). MS m/z (%): $M^{+\cdot}$ 182 (90), 89 (100), 71 (60), 61 (50), 45 (30).

(*E*)-3-Chloro-3-phenyl-2-propenoic acid (2b). m.p. 141–142°C (Lit.[14,15] 142–143°C). ^{1}H NMR ($CDCl_3$): δ 6.38 (s, 1H), 7.45–7.98 (m, 5H), 9.95 (bs, 1H). MS m/z (%): $M^{+\cdot}$ 182 (100), 165 (20), 137 (15), 102 (40), 77 (20),69 (20), 51 (20).

(*Z*)-3-Chloro-2-butenoic acid (2c). m.p. 58°C (Lit.[15,16a,16b] 59°C). ^{1}H NMR ($CDCl_3$): δ 2,23 (s, 3H), 6.06 (s, 1H), MS m/z (%): $M^{+\cdot}$ 120 (100), 104 (20), 102 (40), 84 (80).

(E)-3-Chloro-2-butenoic acid (2c). m.p. 92°C (Lit.[15,16a,16b] 94°C). ^{1}H NMR ($CDCl_3$): δ 2,58 (s, 3H). 6.10 (s, 1H). MS m/z (%): $M^{+\cdot}$ 120 (100), 104 (20), 102 (40), 84 (80).

Ethyl-(*Z*)-3-chloro-3-phenyl-2-propenoate (3a).[17] A pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H) 4.25 (q, 2H), 6.52 (s, 1H), 7.27–7.75 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.22, 60.60, 116.45, 127.20, 128.62, 130.71, 137.20, 146.10, 164.13.

Ethyl-(*E*)-3-chloro-3-phenyl-2-propenoate (3a).[17] A pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.11 (t, 3H), 4.18 (q, 2H), 6.35 (s, 1H), 7.30–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.82, 60.60, 119.95, 127.90, 128.55, 129.92, 136.60, 149.75, 163.7.

(*Z*)-3-Chloro-3-phenyl-N-pyrrolidyl-2-propenamide (4a).[18] A pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.92 (m, 4H), 3.52–3.54 (m, 4H), 6.60 (s, 1H), 7.40–7.60 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 24.40, 25.90, 45.52, 46.90, 120.70, 126.75, 128.55, 129.80, 136.90, 138.38, 164.05; HRMS-EI, m/z (M^+) 235.0770. Calcd. for $C_{13}H_{14}ClNO$ 235.0764.

(*E*)-3-Chloro-3-phenyl-N-pyrrolidyl-2-propenamide (4a).[18] A pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.70–1.72 (m, 4H), 3.10–3.11 (m, 4H), 6.43 (s, 1H), 7.40–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 24.10, 25.70, 45.50, 47.00, 122.90, 128.15, 128.20, 129.80, 136.40, 136.88, 163.85; HRMS-EI, m/z (M^+) 235.0770. Calcd. for $C_{13}H_{14}ClNO$ 235.0764.

(*Z*)-3-Chloro-3-phenyl-N-piperidyl-2-propenamide (4b). A pale yellow oil. IR, neat, (ν, cm^{-1}): 1630 (C═O), 1556 (C═C). ^{1}H NMR ($CDCl_3$): δ 1.55–1.59 (m, 6H), 3.43–3.44 (m, 2H), 3.59–3.62 (m, 2H), 6.56 (s, 1H), 7.30–7.32 (m, 3H), 7.57–7.59 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 24.60, 25.49, 26.64, 42.41, 47.49, 120.47, 126.59, 128.53, 129.71, 136.38, 136.71 164.28. HRMS-EI m/z(M^+) 249.0869. Calcd. for $C_{14}H_{16}ClNO$ 249.0920.

(*Z*)-3-Chloro-3-phenyl-N,N-diethyl-2-propenamide (4c). A white solid m.p. 39–40°C. IR, KBr, (ν, cm^{-1}): 1632 (C═O), 1560 (C═C). ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H), 3.48 (q, 4H), 6.0 (s, 1H), 7.33–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 12.90, 14.50, 42.64, 39.26, 120.61, 126.68, 129.75,

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136.59, 137.06, 165.23. HRMS-EI m/z (M^+) 237.0194. Calcd. for $C_{13}H_{16}ClNO$ 237.0190.

(*Z*)-3-Chloro-3-phenyl-N-(−)-1-phenylethyl-2-propenamide (4d). A white solid m.p. 98–100°C. IR, KBr (ν, cm^{-1}): 1635 (C═O),1568 (C═C). ^1H NMR ($CDCl_3$): δ 1.39 (d, 6H), 5.0 (q, 1H), 6.91 (s, 1H), 7.36–7.46 (m, 10H), 8.65–8.67 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.90, 49.27, 121.23, 126.32, 127.06, 127.39, 127.54, 128.67, 128.80, 130.26, 130.90, 137.09, 138.94, 142.89, 163.00 HRMS-EI, m/z (M^+) 285.0844. Calcd. for $C_{17}H_{16}ClNO$ 285.0847 $[\alpha]_{546}$ −5.0 (c, 1.3 mg/mL, MeOH).

(*Z*)-3-Chloro-N-pyrrolidyl-2-butenamide (4e). A pale yellow oil IR, neat (ν, cm^{-1}): 1650 (C═O), 1560 (C═C). ^1H NMR ($CDCl_3$): δ 1.74–1.85 (m, 4H), 2.40 (s, 3H), 3.34–3.37 (m, 4H), 6.13 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.48, 24.29, 26.07, 28.18, 120.36, 147.09, 163.27. HRMS-EI m/z (M^+) 173.0770. Calcd. for $C_8H_{12}ClNO$ 173.0775.

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