Solvent-free Route to β-Enamino Dichloromethyl Ketones and Application in the Synthesis of Novel 5-Dichloromethyl-1*H*-pyrazoles

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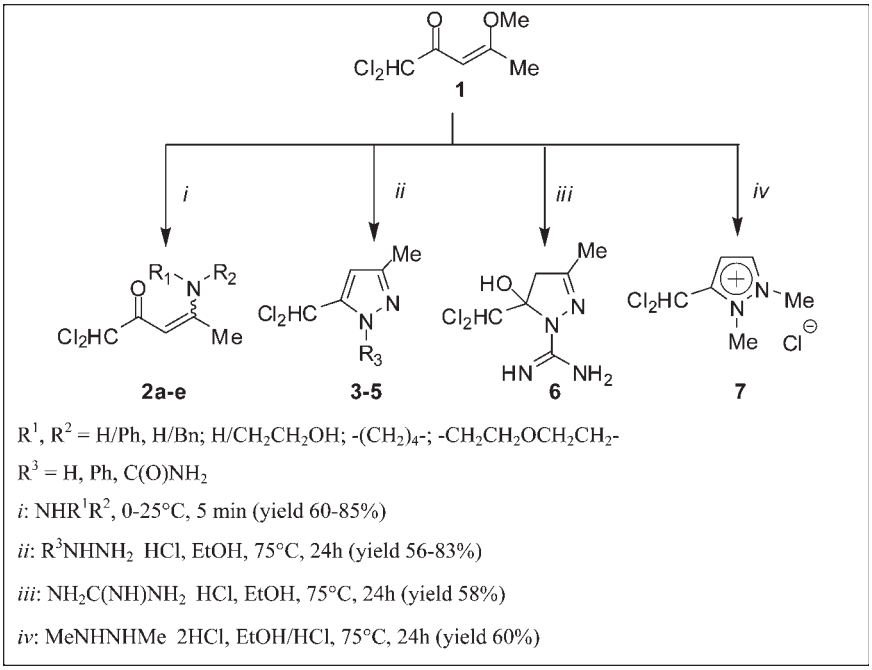

An efficient procedure to prepare a series of five 4-amino-1,1-dichloro-3-penten-2-ones [$CHCl_2C(O)CH{=}C(Me)NR^1R^2$, where R^1/R^2 = H/Ph, H/Bn, H/CH_2CH_2OH, $-(CH_2)_4-$, $-(CH_2)_2O(CH_2)_2$] from the solvent-free reaction of 1,1-dichloro-4-methoxy-3-penten-2-one with primary and secondary amines is reported. 1,1-Dichloro-4-methoxy-3-penten-2-one was reacted with hydrazine hydrochloride, phenylhydrazine hydrochloride and semicarbazide hydrochloride to obtain 5-dichloromethyl-3-methylpyrazoles. Aminoguanidine hydrochloride and 1,2-dimethylhydrazine dihydrochloride were also reacted with 1,1-dichloro-4-methoxy-3-penten-2-one to obtain 5-dichloromethyl-3-methylpyrazoline and 5-dichloromethyl-1,2,3-trimethyl pyrazolium chloride, respectively. All cyclocondensation reactions were performed in one-pot procedures.

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INTRODUCTION

Substituted pyrazoles are important synthetic targets in the pharmaceutical industry because the pyrazole motif makes up the core structure of numerous biologically active compounds, including blockbuster drugs such as Celecoxib [1] and Sildenafil [2]. Specifically, 5-hydroxy-4,5-dihydro-1*H*-pyrazoles are known to possess anti-inflammatory and analgesic activity [3,4]. Although numerous methods have been developed, regioselective synthesis of the pyrazole ring remains a significant challenge for organic chemists. For example, the prevalent method of reacting hydrazines with 1,3-dicarbonyl compounds often results in a mixture of regioisomers when the reactivity of the two carbonyl groups is not drastically different. A modification of this method, replacing 1,3-dicarbonyl compounds with α,β-unsaturated ketones

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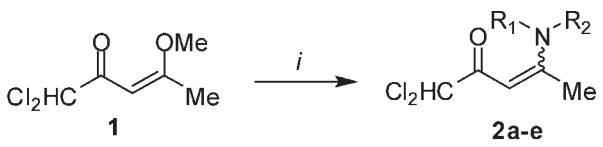
Scheme 1. *i*: NHR^1R^2, 0–25°C, 5 min.



Product	R^1	R^2	Yield[a] (%)
2a	H	Ph	83
2b	H	Bn	68
2c	H	$-CH_2CH_2OH$	78
2d		$-(CH_2)_4-$	60
2e		$-(CH_2)_2O(CH_2)_2-$	85

[a]Yields of isolated products

or esters affords products with higher regioselectivity [5]. Over the last twenty years, our research group has developed a general procedure for preparing β-alkoxyvinyl halomethyl ketones from the β-haloacetylation of enol ethers using functionalized acyl groups RCO (with R = CF_3, CCl_3 and $CHCl_2$) [6,7], and demonstrated their importance in the construction of halomethyl-heterocyclic rings [6–11]. Our results have shown that the reaction of β-alkoxyvinyl trihalomethyl ketones and hydrazines generally produces highly regioselective 5-hydroxy-4,5-dihydro-1*H*-pyrazoles. Although trihalomethyl pyrazolium chlorides have been synthesized by the cyclocondensation reaction of 4-alkoxy-1,1,1-trichloro-3-alken-2-ones with 1,2-dimethylhydrazine [12], they remain rare in the literature. The reactivity of β-alkoxyvinyl dichloromethyl ketones with amines to obtain enaminones and reactions with different hydrazines in an attempt to obtain the respective 5-dichloromethylpyrazoles and 5-dichloromethylpyrazolium has not yet been studied. There is only one report in the literature concerning the reactivity of these compounds with hydroxylamine, and scarce reports on their reaction with amines [13].

In the last few years, our research group has been interested in developing environmental alternatives to obtain heterocyclic building blocks and heterocycles. More recently, we have employed ionic liquids for this objective [13–17]. We have also developed synthetic methods under solvent-free conditions to obtain enaminones [13,18] and 5-hydroxy-4,5-dihydro-1*H*-pyrazoles [19]. Considering our interest in new and green routes in organic synthesis, we have investigated the synthesis of β-enamino dichloromethyl ketones by the solvent-free reaction of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones with primary and secondary amines. In addition, we have studied the cyclocondensation reaction of dichloromethyl substituted α,β-unsaturated ketone with hydrazines in environmentally favorable conditions.

RESULTS AND DISCUSSION

The starting material, 1,1-dichloro-4-methoxy-3-penten-2-one **1**, was synthesized from the reaction of 2-methoxypropene with dichloroacetyl chloride, by methodologies developed in our laboratories [6,20,21]. The synthetic method used to obtain β-enamino dichloromethyl ketones presented in this article was based on the solvent-free reaction of 1,1-dihalo-4-methoxy-3-penten-2-one with amines. The typical experiment was carried out through the addition of the appropriate amine to 1,1-dichloro-4-methoxy-3-penten-2-one **1** at 0°C, followed by stirring the reaction mixture at room temperature for 5 min (Scheme 1). The structures of the synthesized compounds were analyzed by ^1H, and ^{13}C NMR spectroscopy and GC-MS spectrometry. Data are reported in the Experimental Section. In every case, the stereochemistry of the 1,1-dichloro-4-methyl-aminopent-3-en-2-ones **2a–e** (Scheme 1) was determined based on ^1H NMR spectroscopy. The chemical shift of the enamino hydrogen (NH) was observed at 10–12 ppm, which further confirms the *Z*-configuration for the enaminones **2a–c**. This configuration is stabilized by the intramolecular hydrogen bond between the NH and the carbonyl oxygen [13,18]. The *E*-configuration of enaminones **2d–e** was determined by X-ray diffraction. The proposed structure of enaminone **2e** is illustrated in Figure 1.

When the results were compared with those obtained from the same reaction carried out in ionic liquid, the yields (81–88%) and reaction times were similar [13]. For compounds with a trichloromethyl substituent synthesized by this method, the yields were slightly better [18]. Consequently, it was demonstrated that 1,1-dichloro-4-methoxy-3-penten-2-one reacted in good yields with primary and secondary amines in solvent-free conditions.

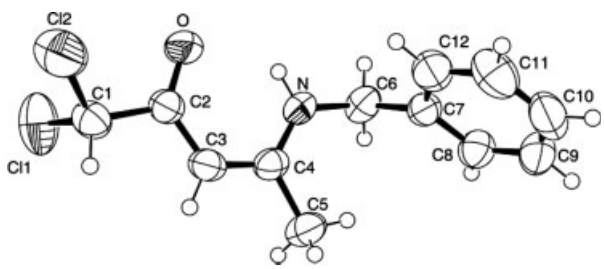
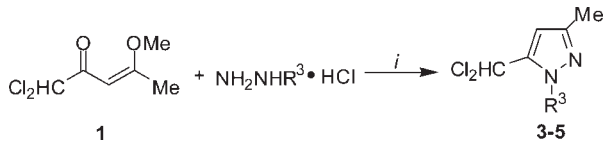


Figure 1. ORTEP of (*E*)-1,1-dichloro-4-morpholin-4-yl-3-penten-2-one (**2e**).

Scheme 2. R = H (83%), Ph (68%), $C(O)NH_2$ (56%), *i*: EtOH, 75°C, 24 h.

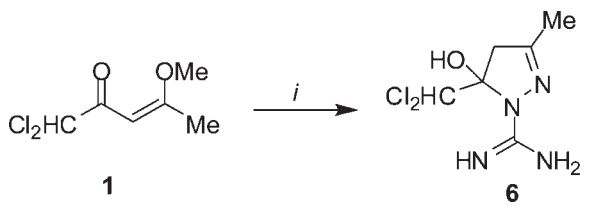


The second part of this study involved the reactivity of 1,1-dichloro-4-methoxy-3-penten-2-one with hydrazines. When 1,1-dichloro-4-methoxy-3-penten-2-one reacted with hydrazine hydrochoride, phenylhydrazine hydrochloride and semicarbazide hydrochloride, the 5-dichloromethyl-3-methylpyrazoles **3–5** (Scheme 2) were obtained. In accordance with previous results published by us, the formation of compound **5** was expected under the conditions used in the present study (refluxing ethanol for 24 h) [22]. On the other hand, the formation of compound **4** with high regioselectivity was unexpected, considering that the reaction of 1,1,1-trihalo-4-methoxy-3-penten-2-ones with phenyl hydrazine resulted in a mixture of isomers when the reaction was carried out in a microwave oven [23]. More surprising was the dehydrated product obtained from the reaction of 1,1-dichloro-4-methoxy-3-penten-2-one with semicarbazide hydrochloride. This result is especially surprising considering the reaction conditions employed in this study because, for the reaction of trihalomethyl precursors the dehydrated product is only obtained after heating 5-trihalomethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole with concentrated sulphuric acid [24]. The yields and reaction conditions are summarized in Scheme 2.

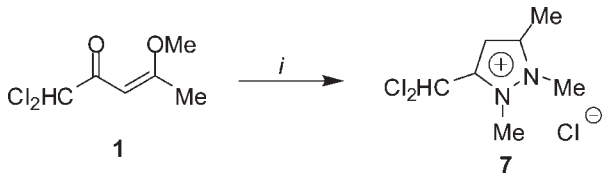
Another dinucleophile evaluated was aminoguanidine hydrochloride, which led to 5-diclorometyl-5-hydroxy-4,5-dihydropyrazoles **6** (Scheme 3), the expected product under the reaction conditions used [25]. The pair of doublets (H4) for geminal protons observed in ^{1}H NMR spectra appeared at 3.4 and 3.6 ppm, with J = 19.5 Hz, which is typical spectroscopic data for 4,5-dihydropyrazoles [17,19,25]. Compound **6** is stable and was not converted to the corresponding pyrazole derivative.

In the same context, 5-dichloromethyl-1,2,3-trimethyl pyrazolium chloride **7** (Scheme 4) was formed from the reaction of 1,1-dichloro-4-methoxy-3-penten-2-one **1** with 1,2-dimethylhydrazine dihydrochloride in the presence of hydrochloric acid as a catalyst and ethanol as solvent. The reaction mixture was stirred at reflux temperature for 24 h. There is little information on the synthesis of these compounds using cyclocondensation methods such as the reaction of a β-diketone derivative with 1,2-dialkylhydrazines [26]. In addition, the most important route to synthesis of 1,2-dialkylpyrazolium salts is the *N*-alkylation of pyrazoles [27].

Scheme 3. *i*: $NH_2C(NH)NH_2$ • 2HCl, EtOH, 75°C, 24h, 58%.



Scheme 4. *i*: MeNHNHMe • 2HCl, EtOH/HCl 1:1, 75°C, 24h, 60%.



In conclusion, this article has demonstrated that 1,1-dichloro-4-methoxy-3-penten-2-one reacted with amines in solvent-free conditions to result in enaminones in good yields. In addition, they were reacted with hydrazines under mild reaction conditions furnishing products with high regioselectivity and in some cases led to unexpected products. Thus, we have demonstrated that the presence of the dichloromethyl group is a determining factor in the regiochemistry of the reaction because it provides a good deal of stability for the intermediate 5-dicloromethyl-5-hydroxy-4,5-dihydropyrazole, which contributes for high regioselectivity.

EXPERIMENTAL

General procedures. Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz) 298 K, digital resolution of ±0.01 ppm, with 0.1 mol L^{-1} solution in $CDCl_3$, DMSO-$d_6$or H_2D/C_6D_6 as solvent. All spectra were registered in a 5 mm tube, at a natural abundance. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The CG was equipped with a split–splitless, injector, auto sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas.

Synthesis of 4-amino-1,1-dichloro-3-penten-2-ones (2a–e). The appropriate amine (2 mmol) was added to 1,1-dichloro-4-methoxy-3-penten-2-one **1** (2 mmol) at 0°C. The reaction mixture was stirred at room temperature for 5 min. The residue was extracted with dichloromethane, dried over anhydrous ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product **2e** was obtained with good purity, and the solids' products **2a–d** were recrystallized from hexane/ethyl acetate 9:1 as solvent.

Synthesis of 5-dichloromethyl-3-methylpyrazoles (3–5) and 5-dichloromethyl-3-methylpyrazoline (6). The appropriate hydrazine (2 mmol) was added to a solution of 1,1-

dichloro-4-methoxy-3-penten-2-one **1** (2 mmol) in ethanol (2 mL) at room temperature. The reaction mixture was stirred at reflux temperature for 24 h. The residue was extracted with dichloromethane, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product **4** was obtained with good purity, and the solids products **3** and **5–6** were recrystallized from ethanol as solvent.

Synthesis of 5-dichloromethyl-1,2,3-trimethyl pyrazolium chloride (7). 1,2-dimethylhydrazine dihydrochloride (2 mmol) and 36% hydrochloric acid (2 mL) were added to a solution of 1,1-dichloro-4-methoxypent-3-en-2-one **1** (2 mmol) in ethanol (2 mL) at room temperature. The reaction mixture was stirred at reflux temperature for 24 and the byproducts were extracted with dichloromethane. The product **7** was obtained in good purity from the aqueous phase after evaporation of water under vacuum.

(*Z*) 1,1-Dichloro-4-phenylaminopent-3-en-2-one (2a). $C_{11}H_{11}Cl_2NO$ Mol. Wt.: 244.12 (83%); mp 63–65°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.08 (s, 3H, H5), 5.56 (s, 1H, H3), 5.90 (s, 1H, H1), 7.20–7.40 (m, 5H, Ph), 12.32 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1 (C5), 70.3 (C3), 91.0 (C1), 124.9, 126.7, 129.2, 137.3, 165.9 (C4), 184.6 (C2); *m*/*z* 243 (M^+, 31%), 160 (100), 144 (43), 77 (64).

(*Z*) 4-Benzylamino-1,1-dichloropent-3-en-2-one (2b). $C_{12}H_{13}Cl_2NO$ Mol. Wt.: 258.15 (68%); mp 72–74°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.07 (s, 3H, H5), 4.50 (d, J = 5.9 Hz, 2H, CH_2), 5.41 (s, 1H, H3), 5.85 (s, 1H, H1), 7.30–7.40 (m, 5H, Ph), 11.11 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.3 (C5), 47.2 (CH_2), 70.4 (C3), 80.7 (C1), 126.8, 127.7, 128.8, 136.3, 168.0 (C4), 183.8 (C2); *m*/*z* 257 (M^+, 24%), 174 (98), 91 (100), 65 (49).

(*Z*) 1,1-Dichloro-4-(2-hydroxyethylamino)-pent-3-en-2-one (2c). $C_7H_{11}Cl_2NO_2$ Mol. Wt.: 212.07 (78%); mp 70–72°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.09 (s, 3H, H5), 3.50 (t, J = 5.6 Hz, 2H, CH_2), 3.80 (t, J = 5.2 Hz, 2H, CH_2), 5.36 (s, 1H, H3), 5.84 (s, 1H, H1), 10.96 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6 (C5), 45.7 (CH_2), 60.9 (CH_2), 70.6 (C3), 89.8 (C1), 168.9 (C4), 183.3 (C2); *m*/*z* 211 (M^+, 15%), 128 (100), 82 (24).

(*E*) 1,1-Dichloro-4-(pyrrolidin-1-yl)-pent-3-en-2-one (2d). $C_9H_{13}Cl_2NO$ Mol. Wt.: 222.11 (60%); mp 112–113°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.94–2.12 (m, 4H, 2 × CH_2), 2.57 (s, 3H, H5), 3.39 (t, J = 6.1 Hz, 2H, CH_2), 3.52 (t, J = 5.9 Hz, 2H, CH_2), 5.25 (s, 1H, H3), 5.80 (s, 1H, H1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.9 (C5), 24.6 (CH_2), 24.9 (CH_2), 48.5 (CH_2), 48.7 (CH_2), 72.5 (C3), 87.8 (C1), 164.6 (C4), 182.6 (C2); *m*/*z* 221 (M^+, 25%), 138 (100), 70 (37).

(*E*) 1,1-Dichloro-4-(morpholin-4-yl)-pent-3-en-2-one (2e). $C_7H_{11}Cl_2NO$ Mol. Wt.: 238.11 (85%) Mp 96–98°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.56 (s, CH_3), 3.51 (qua, 2 × CH_2), 3.76 (qua, 2 × CH_2), 5.53 (s, CH), 5.79 (s, CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.1 (CH3), 46.5 (CH_2), 66.1 (CH_2), 72.4 (C), 88.7 (CH), 165.9 (CH), 184.4 (C=O); *m*/*z* 237 (M^+, 6%), 154 (100), 55 (33), 96 (22), 174 (12), 126 (7), 202 (5). Crystallographic data for **2e** were deposited at the Cambridge Crystallographic Data Center (CCDC 649396). Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: ±44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

5-Dichloromethyl-3-methyl-1*H*-pyrazole (3). $C_5H_6Cl_2N_2$ Mol. Wt.: 165.02 (83%); mp 89–90°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3), 6.28 (s, 1H, CH), 6.74 (s, 1H, $CHCl_2$), 8.15 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (CH_3), 69.0 ($CHCl_2$), 105.6 (C4), 142.9 (C5), 143.0 (C3); *m*/*z* 164.1 (M^+, 13%), 149.1 (100), 109.1 (22).

5-Dichloromethyl-3-methyl-1-phenyl-1*H*-pyrazole (4). $C_{11}H_{10}Cl_2N_2$ Mol. Wt.: 241.12 (68%); oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3), 6.57 (s, 1H, CH), 6.65 (s, 1H, $CHCl_2$), 7.43–7.52 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 61.1 ($CHCl_2$), 107.5 (C4), 125.9, 128.9, 129.4, 138.3, 142.3 (C5), 149.5 (C3); *m*/*z* 240 (M^+, 36%), 205.1 (73), 169.1 (100).

1-Carboxamide-5-dichloromethyl-3-methyl-1*H*-pyrazole (5). $C_6H_7Cl_2N_3O$ Mol. Wt.: 208.05 (46%); mp 110–111°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H, CH_3), 6.41 (s, 1H, CH), 7.76 (s, 1H, $CHCl_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2 (CH_3), 64.3 ($CHCl_2$), 107.3 (C4), 145.2 (C5), 151.7 (C3), 152.6 [C(O)NH_2]; *m*/*z* 207 (M^+, 84%), 191 (38), 161 (62), 133 (100), 115 (85).

1-Carboximidamide-5-dichloromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazole (6). $C_6H_{10}Cl_2N_4O$ Mol. Wt.: 225.08 (58%); mp 68–70°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.08 (m, 3H, CH_3), 3.61 (d, J = 19.6 Hz, 1H, H4a), 3.38 (d, J = 19.4 Hz, 1H, H4b), 7.89 (s, 1H, $CHCl_2$), 9.01 (br s, 3H, 3 × NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 15.7 (CH_3), 47.2 (C4), 73.0 ($CHCl_2$), 96.7 (C5), 152.5 (C3), 158.7 [C(NH)NH_2].

5-Dichloromethyl-1,2,3-trimethyl pyrazolium chloride (7). $C_7H_{11}Cl_3N_2$ Mol. Wt.: 229.54 (60%); mp 112–113°C; ^{1}H NMR (200 MHz, H_2O/C_6D_6) δ 2.73 (s, 3H, CH_3), 4.22 (s, 3H, CH_3), 4.34 (s, 3H, CH_3), 7.19 (s, 1H, CH), 7.58 (s, 1H, $CHCl_2$); ^{13}C NMR (50 MHz, H_2O/C_6D_6) δ 11.9 (CH_3), 34.2 (CH_3), 35.4 (CH_3), 59.9 ($CHCl_2$), 107.5 (C4), 145.4 (C5), 147.6 (C3); *m*/*z* 193 (M–Cl, 59%), 156 (100), 129 (39).

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