Trichloronitromethane with Acyl Chlorides in the Presence of Tin(II) Chloride: Synthesis of Trichloronitro Ketones

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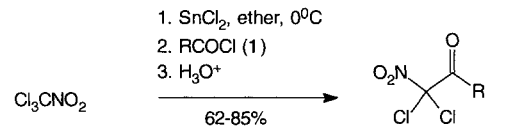
Trichloronitromethane adds to acid chlorides in the presence of tin(II) chloride to yield dichloronitro ketones via a substitution reaction. Reduction and dechlorination of the dichloronitro ketones give dichloroamino alcohols and nitro ketones, respectively, in good yield.

Trichloronitromethane is used generally as a repellent, fumigant, insecticide, and disinfectant[1-6]. The trichloronitromethane molecule contains only one carbon atom and represents a very convenient C-1 synthon.[7] Three halogens and one nitro unit give this synthon several advantages relative to other C-1 synthons. As the nitro group can be reduced to an amino group, the dichloronitro alcohols are useful substrates for the preparation of amino alcohols, some of which are biologically important. Nitro alcohols containing halogen have antimicrobial activity that inhibits the growth of a broad range of organisms.[8-11] In addition to this property, the halogen atoms can be replaced with other groups to obtain functionalized derivatives. In the literature,[12] most C–C bond forming reactions that utilize nitroalkanes make use of the activity of the α-protons via deprotonation. In this work, we report that trichloronitromethane can be used as a d^1 synthon and the reaction of trichloronitromethane with acyl chlorides gives the corresponding dichloronitro ketones in good yield. There are many methods for the formation of ketones from acyl chlorides. Among these methods is formation of Grignard reagents in the presence of iron(III) chloride,[13-14] iron(III) acetoacetate,[15] copper halide,[16-18] copper–copper chloride complex,[19] or vanadium chloride.[20] Other methods involve the use of organocadmium,[21] organolithium,[22] samarium iodide,[23] and alkyllithium cuprate[24-25] reagents. For the formation of ketones, many catalysts such as palladium diacetate, aluminium chloride, zinc chloride, titanium chloride, bistriphenyl phosphine palladium dichloride have been used.[26-30] In all cases, the compounds have at least one α-hydrogen.

In our earlier work we reported[31] Reformatsky-like reaction of trichloronitromethane with aldehydes in the presence of tin(II) chloride to give dichloronitro alcohols. In the present work, the same reaction was carried out with acyl chlorides instead of aldehydes in order to obtain polyfunctional ketones.

As shown in Scheme 1, trichloronitromethane was reacted with acetyl chloride and tin(II) chloride in diethyl ether at 0 °C for 40 minutes. After hydrolysis 1,1-dichloro-1-nitropropan-2-one **(2a)** was obtained in 65% yield.

The ^{1}H NMR spectrum of compound **2a** showed a singlet at $\delta = 2.10$ (CH_3 shifted from $\delta = 2.83$ to 2.10). The ^{13}C NMR spectra of **2a** showed an additional peak arising from a new tertiary carbon atom at $\delta = 132.5$. Various

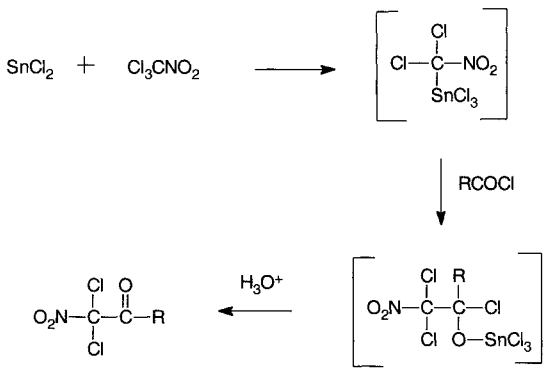


1,2	R	1,2	R
a	Me	f	Ph
b	CH_2Cl	g	2,4-dichlorophenyl
c	Et	h	4-*n*-pentyloxyphenyl
d	*i*-Pr	i	2-furyl
e	2-thiophenyl		

Scheme 1

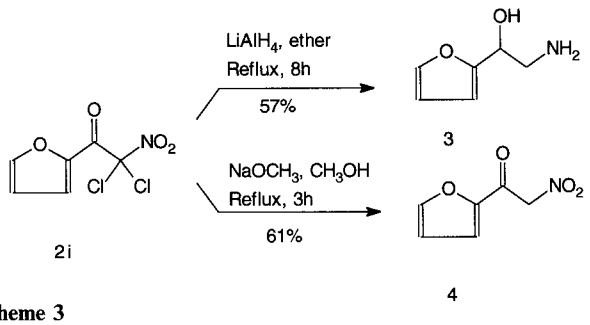
aliphatic and aromatic acyl chlorides were reacted with trichloronitromethane in the presence of tin(II) chloride in the same fashion, and the results are summarized in Scheme 1.

For the reaction of trichloronitromethane with acyl chlorides in the presence of tin(II) chloride, two different protocols have been followed. One protocol involved the injection of trichloronitromethane into a mixture of tin(II) chloride and acyl chlorides at 0 °C. The other protocol was the injection of acyl chloride into the remaining components of the reaction mixture. In both cases, no effect on yield and product formation could be observed. The best results were obtained when the ratio of the reactants was 1:2:1 (carbonyl compound–tin(II) chloride–trichloronitromethane). This reaction presumably involved the reaction of tin(II) chloride with a halo group α to the nitro group to give an organometallic intermediate. The equation given in Scheme 2 shows the suggested mechanism for this reaction.



Scheme 2

As a representative example, reduction and dechlorination reactions were carried out with 2,2-dichloro-1-(2-furyl)-2-nitroethanone **(2i)**. As shown in Scheme 3, the ketone **2i** was reacted with $LiAlH_4$ in Et_2O. After hydrolysis and purification, 2-amino-1-(2-furyl)ethanol **(3)** was obtained in 57% yield. The dechlorination reaction was also carried out with ketone **2i**. The reaction of ketone **2i** with NaOMe in methanol gave 1-(2-furyl)-2-nitroethanone **(4)** in 61% yield.



Scheme 3

As can be seen from the results, trichloronitromethane is a valuable C-1 unit in C–C bond forming reactions via the formation of polyfunctional ketones starting from nonfunctional or functional acyl chlorides. Functionalities present in these ketones may be suitable for a wide range of other chemical manipulations.

All reagents were of commercial quality, and reagent quality solvents were used without further purification. IR spectra were determined on a Philips PU9700 spectrometer. ^{1}H NMR spectra were determined on a Bruker AC 80 MHz FT spectrometer. GC analyses were determined on a HP 5890 apparatus. Mass spectra were obtained on VG Trio2 spectrometer at ionization energy of 70 eV. The elemental analyses were performed at the Middle East Technical University Analysis center. Compounds **2a–i** and **4** gave C,H analysis $\pm$ 0.34%; except **2e**, C $\pm$ 0.41%.

Dichloronitro Ketones 2; General Procedure:
$SnCl_2$ (1.9 g, 10 mmol) in Et_2O (40 mL) was added to 5 mmol of trichloronitromethane (0.82 g) in Et_2O (1 mL) at 0°C. Acyl chlorides (5 mmol) were added and the mixture was stirred for 40 min to 4 h (TLC control). The reaction mixture was diluted with Et_2O (50 mL). The Et_2O layer was washed with 1 M aq HCl, H_2O, sat. aq Na_2CO_3, brine, and dried ($MgSO_4$). The product was purified by column chromatography on Merck silica gel using EtOAc/hexane.

1,1-Dichloro-1-nitropropan-2-one **(2a)**:
Oil, 558 mg, 65% yield. Purified by chromatography (EtOAc/hexane, 1:4).
IR (neat): ν = 2980–2880, 1710, 1585, 1400, 1150 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 2.10 (s, 3H, CH_3).
^{13}C NMR ($CDCl_3$): δ = 20.05 (CH_3), 132.5 (CCl_2NO_2), 175.5 (CO).

1-Nitro-1,1,3-trichloropropanone **(2b)**:
Oil, 635 mg, 62% yield. Purified by chromatography (EtOAc/hexane, 1:4).
IR (neat): ν = 2980–2850, 1700, 1580, 1310, 1100 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 3.91 (s, 2H, CH_2).
MS: m/z = 205 (M^+).

1,1-Dichloro-1-nitrobutan-2-one **(2c)**:
Oil, 705 mg, 76% yield. Purified by chromatography (EtOAc/hexane, 1:3).
IR (neat): ν = 3000–2850, 1740, 1490, 1390, 1200, 1050 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3H, J = 6 Hz, CH_3), 2.23–2.61 (m, 2H, CH_2).

1,1-Dichloro-3-methyl-1-nitrobutan-2-one **(2d)**:
Oil, 810 mg, 81% yield. Purified by chromatography (EtOAc/hexane, 1:4).
IR (neat): ν = 2990–2810, 1710, 1580, 1390, 1100 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.34 (d, 6H, J = 8 Hz, Me_2), 2.34–2.68 (m, 1H, CH).
^{13}C NMR ($CDCl_3$): δ = 20.06 (CH_3), 45.5 (CH), 137.5 (Cl_2CNO_2), 175.7 (CO).
MS: m/z = 200 (M^+).

2,2-Dichloro-2-nitro-1-(2-thiophenyl)ethanone **(2e)**:
Oil, 790 mg, 66% yield. Purified by chromatography (EtOAc/hexane, 1:3).
IR (neat): ν = 2980–2880, 1680, 1480, 1350, 1100 cm^{-1}
^{1}H NMR ($CDCl_3$): δ = 7.15–7.33 and 7.84–8.15 (m, 3H_{arom}).

2,2-Dichloro-2-nitro-1-phenylethanone **(2f)**:
Oil, 990 mg, 85% yield. Purified by chromatography (EtOAc/hexane, 1:3).
IR (neat): ν = 3010–2900, 1710, 1585, 1510, 1390, 1200 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 7.41–7.62 and 7.89–8.21 (m, 5H_{arom}).

2,2-Dichloro-1-(2,4-dichlorophenyl)-2-nitroethanone **(2g)**:
Oil, 1.11 g, 74% yield. Purified by chromatography (EtOAc/hexane, 1:3).
IR (neat): ν = 3050–2910, 1750, 1570, 1380, 1210 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 7.26–7.50 (m, 2H_{arom}), 7.85–8.15 (m, 1H_{arom}).
MS: m/z = 302 (M^+).

2,2-Dichloro-2-nitro-1-(4-n-pentyloxyphenyl)ethanone **(2h)**:
Oil, 1.32 g, 83% yield. Purified by chromatography (EtOAc/hexane, 1:2).
IR (neat): ν = 2990–2850, 1690, 1580, 1400, 1250, 1150 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3H, J = 6 Hz, CH_3), 1.55–2.10 (m, 6H, 3CH_2), 4.12–4.44 (m, 2H, OCH_2), 7.15–8.25 (m, 4H_{arom}).

2,2-Dichloro-1-(2-furyl)-2-nitroethanone **(2i)**:
Oil, 810 mg, 78% yield. Purified by chromatography (EtOAc/hexane, 1:4).
IR (neat): ν = 2980–2880, 1720, 1590, 1480, 1400, 1260 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 6.61 (m, 1H_{arom}), 7.54 (m, 1H_{arom}), 7.83 (m, 1H_{arom}).

2-Amino-1-(2-furyl)ethanol (3):
Compound **2i** (0.50 g, 2.4 mmol) in 40 mL of dry Et_2O was added to $LiAlH_4$ (0.42 g, 11.15 mmol) in 15 mL of dry Et_2O and refluxed for 8 h (checked by TLC; EtOAc). The reaction mixture was hydrolyzed with EtOAc (40 mL) and water (20 mL) was added. The organic phase was separated and washed with brine (30 mL), dried ($MgSO_4$) and filtered. After the solvent was removed under reduced pressure, the crude product was purified by flash column chromatography (silica gel; EtOAc). The product was isolated in 57% yield (174 mg) as a colorless solid mp 85–87°C (Lit.[32] 83–84°C).
IR (KBr): ν = 3600–3350, 2980–2800, 1590, 1260 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 2.21 (br s, 2H, NH_2), 4.51 (s, 2H, CH_2), 6.21–6.45 (m, 2H, C-3, C-4H), 7.31 (br s, 1H, C-5H).
^{13}C NMR ($CDCl_3$): δ = 55.2 (CH_2), 95.7 (CHOH), 105.7 (C-2_{ring}), 108.2 (C-3_{ring}), 136.4 (C-4_{ring}), 148.5 (C-5_{ring}).
MS [$C_6H_9NO_2$ (127.14)]: m/z = 127 (M^+).

1-(2-Furyl)-2-nitroethanone (4):
To Na (115 mg, 5 mmol) 5 mL of MeOH was added slowly and refluxed for 30 min. To this mixture was added **2i** (0.5 g, 2.4 mmol) in 0.5 mL of MeOH dropwise and refluxed for 3 h (checked by

TLC; silica gel; EtOAc/hexane, 1:4). The mixture was cooled to r.t., hydrolyzed with water (10 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was washed with water (2 × 25 mL), brine (25 mL), dried ($MgSO_4$) and filtered. After the solvents were removed under reduced pressure, the crude product was purified by flash column chromatography (silica gel; EtOAc/hexane, 1:4). Pure nitro ketone **4** was isolated in 61% (227 mg) yield as an oil.

(IR (neat): ν = 2940–2850, 1720, 1490, 1200 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.91 (s, 2H, CH_2), 6.68 (dd, J = 1.5, 3 Hz, 1H, C-4H), 7.35 (dd, J = 0.7, 2.6 Hz, 1H, C-3H), 7.75–7.81 (m, 1H, C-5H).

^{13}C NMR ($CDCl_3$): δ = 85.1 (CH_2), 111.8 (C-2_{ring}), 117.2 (C-3_{ring}), 146.4 (C-4_{ring}), 152.5 (C-5_{ring}), 192 (C=O).

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