Reduction cleavage of S–S bond by Zn/Cp_2TiCl_2: application for the synthesis of β-arylthiocarbonyl compounds

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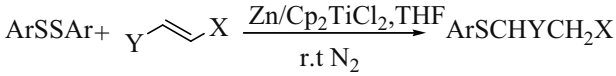
Diaryl disulfides were reduced efficiently by a Zn/Cp_2TiCl_2 system at room temperature in dry THF to give the corresponding nucleophilic sulfur anion–titanocene complex, followed by reaction with α, β-unsaturated esters (ketones or nitriles) to afford the corresponding β-arylthioesters(ketone or nitrile) in good yields.

Keywords: titanocene dichloride, zinc, reduction, diaryldisulfide, β-arylthioesters, β-arylthioketones, β-arylthionitriles

Recently, organic sulfur compounds have become of increasing importance in organic synthesis. As important difunctional compounds and attractive synthetic intermediates in organic synthesis, β-thioesters have received considerable attention.[1,2] The general method for the their preparation is the addition of thiols to acryl esters or acrylonitriles in the presence of sodium ethoxide,[3-5] but this requires strongly basic conditions and the use of toxic and odorous thiols as starting materials. It is well known that diaryl disufides, which are air-stable, of low-toxicity and free of smell, have been in great demand as intermediates to synthesise β-thiocarbonyl compounds. Therefore, sulfur anions are generated in situ *via* reductive cleavage of an S–S bond to avoid handling thiols. Many approaches have been reported for reducing disulfides. Previously, some of the more common reducing agents such as sodium borohydride,[6] lithium aluminum hydride,[7] potassium trrisopropoxy borohydride,[8,9] lithium tris(dialkyl amino)aluminum hydrides,[10] lithium tri-*tert*-butoxyaluminum hydride,[11] triphenyl phosphine,[12] tributyl phosphine[13,14] *etc*. have been used to reductively cleave the S–S bond. Recently, some metals such as In,[15,16] Sn,[17], Sm[18] Cd,[19] or some metal halides such as SmI_2,[20] InI[21] or a the combination of samarium and a metal halide such as Sm/$NiCl_2$[22] and Sm/$CoCl_2$,[23] were reported to cleave S–S bonds efficiently. However, these methods involved using expensive or toxic metals. As it is well known that zinc is an abundant, inexpensive and nontoxic metal in nature, the use of zinc seems to be an attractive possibility to promote this reaction. Some system of zinc/metal halide have been applied to reduce the S–S bond, such as Zn/$TiCl_4$,[24] Zn/$ZrCl_4$,[25] Zn/$CoCl_2$ [26] and Zn/$AlCl_3$.[27] Unfortunately, most of these methods have one or more disadvantages such as: (i) air- or moisture-sensitive reagents; (ii) low yield; (iii) poor chemoselectivity or functional group intolerance. The Cp_2TiCl_2 shows good stability in air and has been widely applied in organic synthesis. The Cp_2TiCl_2/Bu^i MgBr system could efficiently reductively cleave S–S bonds,[28] but this system was highly moisture-sensitive due to the use of the Grignard reagent. It would be ideal if the zinc and Cp_2TiCl_2 could be used together. We report here the reduction of diaryl disulfides by a combined system of Cp_2TiCl_2/Zn for the synthesis of β-arylthiocarbonyl and nitrile compounds.

The experimental procedure is very simple. A mixture of Cp_2TiCl_2 (1.0 mmol) with activated Zn dust (2.0 mmol) in dry THF was stirred at room temperature for 1.0 h, the solution turning to deep green from red-brown due to formation of [Cp_2TiCl]. When disulfide was added to the [Cp_2TiCl]-containing solution, a deep red colour immediately formed. After addition of α, β-unsaturated carbonyl compounds or nitriles to the reaction mixture, it gradually turned red-brown. After hydrolysis and then separation, the target products of β-arylthiocarbonyl compounds or the corresponding nitriles were obtained in good yields (Scheme 1).

The results are shown in Table 1. One can see that the reaction proceeded well for a variety of diaryldisulfides and α,β-unsaturated carbonyl compounds or nitriles, all acrylic esters and acrylonitriles and methyl ethenyl ketones gave the corresponding products in satisfactory yields. The results also revealed that the reaction is not sensitive to the electronic nature of functional groups present in the aryl groups of



Scheme 1 The synthesis of β-arylthio compounds.

Table 1 The synthesis of β-arylthio compounds

Entry	Ar	Y	X	Time/h	M.p./°C	Yield/%
4a	Ph	H	CO_2CH_3	4.0	Oil	92
4b	Ph	H	$CO_2C_2H_5$	4.5	Oil	90
4c	Ph	H	$CO_2C_4H_9$	4.0	Oil	73
4d	Ph	H	$CO_2C_8H_{17}$-*n*	8.0	Oil	68
4e	Ph	CH_3	$CO_2C_2H_5$	5.0	Oil	61
4f	*p*-ClC_6H_4	H	$CO_2C_2H_5$	3.5	80–81[82][5]	85
4g	*p*-CH_3 C_6H_4	H	$CO_2C_2H_5$	4.0	56–57[58][5]	90
4h	*p*-CH_3O C_6H_4	H	$CO_2C_2H_5$	4.5	Oil	87
4i	Ph	H	CN	4.0	Oil	92
4j	*p*-Cl C_6H_4	H	CN	4.5	52–53[54–55][30]	86
4k	*p*-CH_3 C_6H_4	H	CN	5.0	Oil	81
4l	Ph	H	$COCH_3$	1.0	Oil	98

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disulfides. Either electron-donating or electron-withdrawing groups could be substituted leading to the desired products in good yields. A detailed analysis of the results reveals that the product yield of the methyl ethenyl ketones, in which the carbonyl group has stronger electron withdrawing ability, is higher than those of acrylic esters and acrylonitriles. Steric hindrance an influence on the reaction. Compared with the similar substrate unsubstituted at the β-position, the methyl group substituted substrates required a little longer reaction time to give a low yield. The size of the alkyl chain in the ester group also had a significant influence, and as the alkyl chain became longer, the products were obtained in lower yields.

Although further study is necessary to clarify the reaction mechanism, thes results mentioned above suggest that this reaction probably takes place through a reduction mechanism as shown as following (Scheme 2).

The necessary use of zinc indicates the importance of $Cp_2Ti^{III}Cl$ formation, which was actually observed in the reaction mixture. Because the formation of $Cp_2TiCl(OH)$, the Cp_2TiCl_2 cannot be regenerated at the final step. Two equivalent of Cp_2TiCl_2 should be needed. Therefore, we tried the reaction using a catalytic amount of Cp_2TiCl_2 and found that the reaction actually proceeded inefficiently with only 10% yield of the desired product.

In summary, we have developed a highly efficient method for the reductive cleavage of S–S bond and applied it to the synthesis of β-arylthiocarbonyl and β-thio compounds. It has various merits such as air-stable starting materials, mild and neutral reaction conditions, convenient manipulation and good yields.

Experimental

^{1}H NMR were recorded on INOVA-400 spectrometer, using $CDCl_3$ as the solvent with TMS as an internal standard; IR spectra were determined on Perkin-Elmer 683 spectrophotometer; tetrahydrofuran was distilled from sodium benzophenone. Zinc was activated by dilute acid followed by washing with water and drying.

Typical procedure: To a solution of Cp_2TiCl_2 (0.25 g, 1.0 mmol) in dry THF (6.0 mL) was added Zn dust (0.13 g, 2.0 mmol). The resulted mixture was stirred at room temperature under a N_2 atmosphere for 1.0 h. Then the disulfide (0.5 mmol) was added to the reaction mixture and the solution became a deep red colour. After that, acrylic esters or acrylnitriles or methyl ethenyl ketone (1.0 mmol) was added and resulting mixture was stirred at room temperature under a N_2 atmosphere for a period of time listed in Table 1. Then dilute hydrochloric acid (20 mL. 1.2 M) was added, after usual work-up, the products were purified by preparative TLC on silica gel using light petroleum-ether as eluent (30:1).

$PhSCH_2CH_2CO_2CH_3$:[25] IR(film)ν_{max}(cm^{-1}) 1735; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.20–7.35(m, 5H, C_6H_5), 3.70(s, 3H, CH_3), 3.10(t, J = 7.3 Hz, 2H, Ph$\underline{CH_2}$), 2.70(t, J = 7.3 Hz, 2H, CH_2CO); ^{13}C NMR(100 MHz, $CDCl_3$) 28.7 ($SCH_2\underline{C}H_2$), 33.4(SCH_2), 63.2($CO_2\underline{C}H_3$), 126.8(C_6H_5), 128.3(C_6H_5), 132.4(C_6H_5), 134.2(C_6H_5), 173.2(CO_2).

$PhSCH_2CH_2CO_2CH_2CH_3$:[3] IR(film) ν_{max}(cm^{-1}) 1732; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.20–7.45(m, 5H, C_6H_5), 4.20(q, J = 7.2 Hz, 2H, CO_2CH_2), 3.13(t, J = 7.0 Hz, 2H, SCH_2), 2.63(t, J = 7.0 Hz, 2H, ***CH_2CO_2***), 1.20(t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR(100 MHz, $CDCl_3$): 14.1(CH_3), 29.8 ($\underline{C}H_2CO_2$), 31.4(SCH_2), 61.3 ($CO_2\underline{C}H_2$), 125.2(C_6H_5), 126.8(C_6H_5), 129.0(C_6H_5), 136.4(C_6H_5), 173.1(CO_2).

$PhSCH_2CH_2CO_2CH_2CH_2CH_2CH_3$:[29] IR(film) ν_{max}(cm^{-1}): 1732; ^{1}H NMR ($CDCl_3$, 400 MHz),7.20–7.39(m, 5H, C_6H_5), 4.10(q, J = 6.8 Hz, 2H, CO_2CH_2), 3.18(t, J = 7.4 Hz, 2H, SCH_2), 2.64(t, J = 7.4 Hz, 2H, CH_2CO_2), 1.58–1.67(m, 2H, $\underline{CH_2}CH_2CH_3$), 1.33–1.43(m, 2H $CH_2\underline{CH_2}CH_3$), 0.94(t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 13.7($CH_2CH_2\underline{C}H_3$), 19.1($CH_2\underline{C}H_2CH_3$), 29.1($\underline{C}H_2CH_2CH_3$, 30.6($\underline{C}H_2CO_2$), 34.4(SCH_2), 64.7($CO_2\underline{C}H_2$), 126.5(C_6H_5), 129.1 (C_6H_5), 130.1(C_6H_5), 135.2(C_6H_5), 171.9(CO_2).

$PhSCH_2CH_2CO_2CH_2(CH_2)_6CH_3$:[30] IR(film) ν_{max}(cm^{-1}): 1734; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.37–7.20(m, 5H, C_6H_5), 3.98(t, J = 6.8 Hz, 2H, CO_2CH_2), 3.15(t, J = 7.0 Hz, 2H, SCH_2), 2.65(d, J = 7.0 Hz, 2H, CH_2CO_2), 1.59–1.54(m, 2H, $CO_2CH_2\underline{CH_2}$), 1.37–1.26 (m, 10H, $CO_2CH_2CH_2$ ($\underline{CH_2}$)$_5CH_3$), 0.91(t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 11.3(CH_3), 14.3($\underline{C}H_2CH_3$), 23.6 ($\underline{C}H_2CH_2CH_3$), 23.9 ($CH_2\underline{C}H_2CH_2CH_3$), 28.6($CO_2CH_2\underline{C}H_2CH_2\underline{C}H_2$), 29.6($CO_2CH_2CH_2\underline{C}H_2$), 31.2 ($CO_2CH_2\underline{C}H_2$), 34.6($\underline{C}H_2CO_2$), 38.9 ($SCH_2$), 67.3($CO_2\underline{C}H_2$), 126.8($C_6H_5$), 128.9($C_6H_5$), 130.5($C_6H_5$), 135.6($C_6H_5$), 172.3($CO_2$).

$PhS(CH_3)CHCH_2CO_2CH_2CH_3$:[30] IR(film) ν_{max}(cm^{-1}): 1735; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.42–7.45(m, 2H, C_6H_5), 7.23–7.32(m, 3H, C_6H_5), 4.12(q, J = 7.0 Hz, 2H, CO_2CH_2), 3.58–3.64(m, 1H, CH), 2.62(dd, J = 6.0 Hz, 15.4 Hz, 1H, 1/2CH_2CO_2, 2.43(dd, J = 6.0 Hz, 15.4 Hz, 1H, 1/2CH_2CO_2), 1.32(d, J = 6.4 Hz, 3H, PhS($\underline{CH_3}$) CH), 1.25(t, J = 7.0 Hz, 3H, $CO_2CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2($CO_2CH_2\underline{C}H_3$), 20.9(PhS($\underline{C}H_3$)CH), 39.5(CH_2CO_2), 41.9(CH), 60.6($CO_2\underline{C}H_2$), 127.4(C_6H_5), 128.9(C_6H_5), 132.9(C_6H_5), 133.9(C_6H_5), 171.4(CO_2).

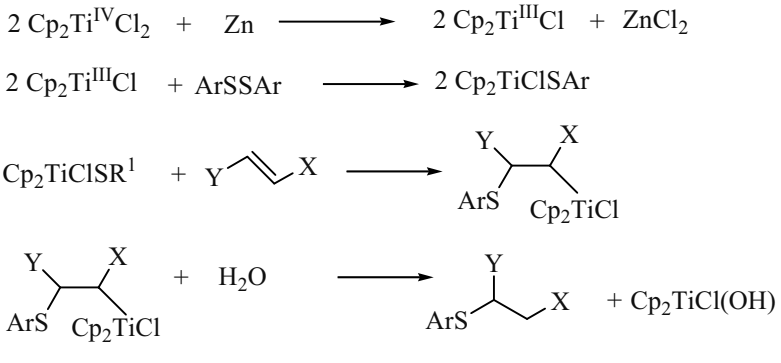
p-$ClC_6H_4SCH_2CH_2CO_2CH_2CH_3$:[5] IR(KBr) ν_{max}(cm^{-1}): 1731; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.26–7.32(m, 4H, *p*-ClC_6H_4), 4.15(q, J = 7.0 Hz, 2H, CO_2CH_2), 3.14(t, J = 7.2 Hz, 2H, S$\underline{CH_2}CH_2$), 2.60(t, J = 7.2 Hz, 2H, $SCH_2\underline{CH_2}$), 1.26(t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz,$CDCl_3$): 14.2(CH_3), 29.3 ($SCH_2\underline{C}H_2$), 34.3(SCH_2), 60.8($CO_2\underline{C}H_2$), 129.1(C_6H_4), 131.5(C_6H_4), 132.6(C_6H_4), 133.8 (C_6H_4), 171.6(CO_2).

p-$CH_3C_6H_4SCH_2CH_2CO_2CH_2CH_3$:[5] IR(film) ν_{max}(cm^{-1}): 1732; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.32(d, J = 8.0 Hz, 2H, C_6H_4), 7.19(d, J = 8.0 Hz, 2H, C_6H_4), 4.15(q, J = 7.2 Hz, 2H, CO_2CH_2), 3.13(t, J = 7.6 Hz, 2H, S$\underline{CH_2}CH_2$), 2.62(t, J = 7.6 Hz, 2H, $SCH_2\underline{CH_2}$), 2.35(s, 3H, *p*-$\underline{CH_3}C_6H_4$), 1.26(t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2(CH_2CH_3), 21.1(*p*-$\underline{C}H_3C_6H_4$), 29.8($SCH_2\underline{C}H_2$), 34.5(SCH_2), 60.7($CO_2\underline{C}H_2$), 129.8(C_6H_4), 131.0(C_6H_4), 131.1(C_6H_4), 136.8(C_6H_4), 171.8(CO_2).

p-$CH_3OC_6H_4SCH_2CH_2CO_2CH_2CH_3$:[5] IR(film) ν_{max}(cm^{-1}) 1736. ^{1}H NMR ($CDCl_3$, 400 MHz), 7.36(d, J = 8.0 Hz, 2H, C_6H_4), 6.86(d, J = 8.0 Hz, 2H, C_6H_4), 4.20(q, J = 6.8 Hz, 2H, CO_2CH_2), 3.80(s, 3H, OCH_3), 3.12(t, J = 7.0 Hz, 2H, S$\underline{CH_2}CH_2$), 2.61(t, J = 7.0 Hz, 2H, $SCH_2\underline{CH_2}$), 1.21(t, J = 6.8 Hz 3H, $CH_2\underline{CH_3}$); ^{13}C NMR(100 MHz, $CDCl_3$): 14.3(CH_3), 31.6($SCH_2\underline{C}H_2$), 34.8(S$\underline{C}H_2CH_2$), 55.8(OCH_3), 61.6($CO_2\underline{C}H_2$), 114.6(C_6H_4), 125.8(C_6H_4), 134.6(C_6H_4), 159.8 (C_6H_4), 171.3(CO_2).

$PhSCH_2CH_2CN$:[4] IR(film) ν_{max}(cm^{-1}): 2250; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.25–7.45(m, 5H, C_6H_5), 3.15(t, J = 7.0 Hz, 2H, SCH_2), 2.55(t, J = 7.0 Hz, 2H, CH_2CN) ^{13}C NMR (100 MHz, $CDCl_3$): 18.3(CH_2CN), 30.2(SCH_2), 118.1(CN), 127.8(C_6H_5), 129.4(C_6H_5), 131.4(C_6H_5), 133.2(C_6H_5).

p-$ClC_6H_4SCH_2CH_2CN$:[4] IR(film) ν_{max}(cm^{-1}): 2244; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.27–7.37(m, 4H, C_6H_4), 3.11(t, J = 6.8 Hz, 2H, SCH_2), 2.59(t, J = 6.8 Hz, 2H, CH_2CN); ^{13}C NMR (100 MHz,



Scheme 2 Proposed mechanism for the synthesis of β-arylthio compounds promoted by the Cp_2TiCl_2/Zn system.

$CDCl_3$): 18.3(CH_2CN), 30.5(SCH_2), 117.8(CN), 129.6(C_6H_4), 131.7(C_6H_4), 132.8(C_6H_4), 134.0(C_6H_4).

p-$CH_3C_6H_4SCH_2CH_2CN$:[4] IR (film) ν_{max}(cm^{-1}): 2250; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.32(d, J = 8.0 Hz, 2H, C_6H_4), 7.15(d, J = 8.0 Hz, 2H, C_6H_4), 3.16(t, J = 7.4 Hz, 2H, SCH_2), 2.55(t, J = 7.4 Hz, 2H, CH_2CN), 2.34(s, 3H, CH_3); ^{13}C NMR (100 MHz,$CDCl_3$): 18.2(CH_3), 21.2(CH_2CN), 30.8(SCH_2), 118.2(CN), 129.3(C_6H_4), 130.2(C_6H_4), 132.3(C_6H_4), 138.2(C_6H_4).

$PhSCH_2CH_2COCH_3$:[31] IR(film) ν_{max}(cm^{-1}): 1707; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.42~7.22 (m, 5H, C_6H_5), 3.76 (t, J = 7.2 Hz, 2H, SCH_2), 3.13 (t, J = 7.2 Hz, 2H,), 2.17(s, 3H, CH_3); ^{13}C NMR(100 MHz, $CDCl_3$): 29.1(CH_3), 31.2($\underline{C}H_2CO$), 34.6(SCH_2), 125.3(C_6H_5), 126.8(C_6H_5), 129.1(C_6H_5), 136.2(C_6H_5), 207.1(CO).

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