

Replacement of the Activated Nitro Group by a Phenylthio Group

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The nitro group, activated by a carbonyl group, alkoxycarbonyl group or a phenyl group, can be replaced by a phenylthio group in the reaction with benzenethiol or its potassium salt. This reaction proceeds in the electron transfer mechanism, and is applicable to the general syntheses of α-phenylthio ketones, α-phenylthio carboxylic esters and α-phenylthio alkylbenzenes from primary nitro compounds.

Primary aliphatic nitro compounds can be prepared in various methods.[1] Recently, the attractive methods of acylation,[2] alkoxycarbonylation,[3] and arylation[4] of the primary nitroalkanes have been reported, and those reactions proceed under mild conditions with high yields due to the strong electron withdrawing inductive effect and the electron acceptability of the nitro group. However, the target molecule in organic synthesis is usually nitro-free one. Therefore, the conversion of the nitro compound into nitro-free one has a considerable value. The replacement of the nitro group by hydrogen is the only useful method which is applicable to α-nitro ketone and α-nitro carboxylic ester.[5] We wish to describe the replacement of the nitro group by a phenylthio group. By this reaction, two-step conversion of primary nitro compound into α-phenylthio ketone, α-phenylthio carboxylic ester and α-phenylthio alkylbenzene become possible (Eq. 1).

$$\underset{\mathbf{1}}{R^1CH_2NO_2} \longrightarrow \underset{\mathbf{2}}{R^1\underset{|}{\overset{}{C}}HNO_2}\ (Y) \longrightarrow \underset{\mathbf{3}}{R^1CHSPh}\ (Y) \qquad (1)$$

$$Y = \overset{O}{\overset{\|}{C}}R^2,\ CO_2R^3,\ Ar$$

In the cases of nitromethane[6] and particular tertiary nitro compound which is active for the S_{RN} type reaction,[7] the replacement of the nitro group by a phenylthio group was already reported. However, these examples are too simple or too unique and not very useful in organic synthesis. As synthetically useful examples, Ono and co-workers recently reported the conversion of allylic nitro compounds into allylic sulfides.[8] Nevertheless, the systems chosen by us are very attractive in organic synthesis.

Results and Discussion

Solvent Effect. Solvent effect was studied for the reaction of 2-nitro-1-phenylethanone with benzenethiol in the presence of azobis(isobutyronitrile)(AIBN). The results were shown in Table 1. When a dipolar aprotic solvent such as hexamethylphosphoric triamide (HMPT), *N,N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) was used, the desired sulfide was obtained. When benzene was used as a solvent, the desired sulfide was not obtained, and a considerable amount of the unreacted starting material remained. The reaction in HMPT gave the best results. Apparently, the order of the reaction rate was HMPT>DMSO>DMF≫benzene, and the yield of the sulfide was in the same order.

Replacement of the Nitro Group Under Neutral Conditions. When α-nitro ketone was treated with benzenethiol (3 equiv) and AIBN (1 equiv) in HMPT at 90 °C for 1 h, the nitro group was replaced by the phenylthio group. It is one of the merits of our method that the conversion can be attained under neutral conditions. This method is suitable for α-nitro ketone, because the C–C bond of α-nitro ketone cleaves easily by nucleophilic attack (Eq. 2). For α-nitrotoluene (**2g**) and methyl nitroacetate (**2f**), too, the replacement proceeded under the same conditions. However, for secondary nitro compounds such as ethyl 2-nitrobutyrate (**2i**) and 1-nitro-1-phenylbutane (**2h**), the yields were much lower (Table 2). Probably this is the limitation of this method.

$$R\overset{O}{\overset{\|}{C}}CH_2NO_2 + Nu^- \longrightarrow R\overset{O}{\overset{\|}{C}}Nu + CH_2NO_2^- \qquad (2)$$

Nu^- = nucleophile

$$\text{neutral:}\quad R\text{-}NO_2 + PhSH \xrightarrow[\text{HMPT}]{\text{AIBN}} R\text{-}SPh + HNO_2 \qquad (3)$$

$$\text{basic:}\quad R\text{-}NO_2 + PhS^- \xrightarrow[\text{HMPT}]{\text{(AIBN)}} R\text{-}SPh + NO_2^- \qquad (4)$$

Table 1. Solvent Effect of the Reaction of **2a** with Benzenethiol in the Presence of AIBN

$$\underset{\mathbf{2a}}{PhC(=O)CH_2NO_2} + \underset{(3\ eq)}{PhSH} \xrightarrow{\text{AIBN}} \underset{\mathbf{3a}}{PhC(=O)CH_2SPh}$$

Solvent	AIBN(equiv)	Conditions	Yield of **3a**/%[a]
HMPT	0.5	90 °C, 0.5 h	56
	0	90 °C, 2 h	35
DMSO	1	90 °C, 8 h	30
DMF	1.5	90 °C, 24 h	29
Benzene	1.5	80 °C, 24 h	Trace[b]

a) Isolated yield. b) A considerable amount of **2a** remained unreacted.

Table 2. Replacement of the Nitro Group by the Phenylthio Group Under Neutral Conditions (Eq. 3)

R-NO_2	AIBN(equiv)	Conditions[a]	Yield of 3/%[b]
2a	0.5	90 °C, 0.5 h,	**3a** 56
	0	90 °C, 2 h,	35
	0[c]	90 °C, 2 h,	0
i-$PrCCH_2NO_2$ **2b** (O)	0.5	90 °C, 1 h,	**3b** 69
i-PrC(=O)-$CHCH_3$ **2c** (NO_2)	1	90 °C, 1 h,	**3c** 61
$(CH_2)_{10}$ ring, C(=O)-CH (NO_2) **2d**	1	90 °C, 1 h,	**3d** 54
CH_3C(=O)-$CHCH_3$ **2e** (NO_2)	1	90 °C, 1 h,	**3e** 47
$O_2NCH_2CO_2CH_3$ **2f**	1.5	130 °C, 0.5 h,	**3f** 55
$PhCH_2NO_2$ **2g**	1	120 °C, 1 h,	**3g** 65
$PhCHCH_2CH_2CH_3$ **2h** (NO_2)	1.5	120 °C, 1 h,	**3h** 13
$CH_3CH_2CHCO_2C_2H_5$ **2i** (NO_2)	1.5	120 °C, 1 h,	**3i** 7

a) 3 equiv of PhSH was used. b) Isolated yield. c) 0.1 equiv of *m*-DNB was added.

Replacement of the Nitro Group Under Basic Conditions. When potassium benzenethiolate was used instead of benzenethiol the replacement also proceeded. This method is favorable for the compounds which do not have the sensitive functionality to a nucleophile. The results are shown in the Table 3. The nitro compound, such as **4**, which was synthesized by the Michael addition of a nitro compound, did not give **5** by the reaction with PhS^-, because retro Michael type elimination predominated and it gave **6** in 61% yield (Eq.5). In order to avoid such elimination, the carbonyl group of **4** must be protected (**2j** in Table 3).

$$\underset{\text{NO}_2}{\overset{\text{O}}{\text{PhCHCH}_2\text{CH}_2\overset{\|}{\text{C}}\text{CH}_3}} \quad \underset{\textbf{4}}{} \quad \not\rightarrow \quad \underset{\text{SPh}}{\overset{\text{O}}{\text{PhCHCH}_2\text{CH}_2\overset{\|}{\text{C}}\text{CH}_3}} \quad \underset{\textbf{5}}{} \quad \rightarrow \quad \underset{\textbf{6}}{\overset{\text{O}}{\text{PhSCH}_2\text{CH}_2\overset{\|}{\text{C}}\text{CH}_3}} \ 61\% \qquad (5)$$

When the nitro compound has an alkoxycarbonyl group, reaction at lower temperatures and addition of AIBN are favorable to avoid the destruction of the alkoxycarbonyl group.

This basic procedure was not appropriate to the replacement of the nitro group of α-nitro ketone due to the nucleophilicity of PhS^- (see Eq. 2), and the yield of the sulfide was lower than that of the neutral procedure (Table 2).

Table 3. Replacement of the Nitro Group by the Phenylthio Group Under Basic Conditions (Eq. 4)

R-NO_2	Conditions	Yield of 3/%[e]
2g	100 °C 1 h	**3g** 77
	120 °C 2.5 h[a]	76
2h	120 °C 2 h	**3h** 72
2i	60 °C 2 h[b]	**2i** 58
$PhCHCH_2CH_2C(O)(O)CH_3$ **2j** (NO_2)	80 °C 3.5 h	**3j** 74
2e	60 °C 1 h[c]	**2e** 17
	60 °C 1 h[c,d]	28

a) 0.1 equiv of *m*-DNB was added. b) 0.25 equiv of AIBN was added. c) 0.5 equiv of AIBN was added. d) Et_3N was used instead of *t*-BuOK. e) Isolated yield.

Mechanism. These reactions (neutral and basic) were accelerated by a small amount of radical initiator such as AIBN, and completely inhibited (neutral) or decelerated (basic) by a small amount of *m*-dinitrobenzene(*m*-DNB). These results and the solvent effect suggest the electron transfer mechanism, which was well established for the replacement of the nitro group.[1] Equations 6—9 show the mechanism of the replacement of the nitro group under basic conditions.

$$PhS^- + R\text{-}NO_2 \longrightarrow PhS\cdot + R\text{-}NO_2^{\cdot-} \quad (6)$$

$$R\text{-}NO_2^{\cdot-} \longrightarrow R\cdot + NO_2^- \quad (7)$$

$$R\cdot + PhS^- \longrightarrow R\text{-}SPh^{\cdot-} \quad (8)$$

$$R\text{-}SPh^{\cdot-} + R\text{-}NO_2 \longrightarrow R\text{-}SPh + R\text{-}NO_2^{\cdot-} \quad (9)$$

However, the mechanism of the reaction under neutral conditions is not apparent. We think, there are two possible mechanisms. One of them involves the equilibrium of Eq 10, followed by Eqs. 6—9. The other one involves the cation radical of benzenethiol which was suggested by Hashiyama and co-workers for the reaction with glycidate.[9] However, we cannot distinguish them up to the present and the mechanism is now under investigation.

$$RhSH \rightleftarrows PhS^- + H^+ \quad (10)$$

$$PhSH + R\text{-}NO_2 \longrightarrow [PhSH^{\cdot+} + R\text{-}NO_2^{\cdot-}] \longrightarrow R\text{-}SPh + HNO_2 \quad (11)$$

Experimental

Materials. Nitro compounds were prepared according to the reported procedures.[1-4,10]

General Procedure for the Replacement of the Nitro Group by a Phenylthio Group Under Neutral Conditions. The nitro compound (3 mmol), benzenethiol (9 mmol) and AIBN (3 mmol) were dissolved in HMPT (7 ml) and the mixture was stirred at 90—130 °C for 0.5—1 h (see Table 2). The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel.

General Procedure for the Replacement of the Nitro Group by a Phenylthio Group Under Basic Conditions. Benezenethiol (9 mmol) and *t*-BuOK (4.5 mmol) were dissolved in HMPT (7 ml), and the nitro compound (3 mmol) was added to that solution and the mixture was stirred at appropriate temperature for 1—3.5 h (see Table 3). The reaction mixture was poured into 0.5 M HCl (30 ml (1 M=1 mol dm^{-3})) and extracted with ether. The organic layer was washed with water, dried with $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel.

Identification of the Sulfides. The sulfides were identified by ^1H NMR and IR spectra. Some of them (**3a**, **3b**, **3d**, **3e**, **3f**, **3g**, and **3i**) were compared with the data reported.[11,12]

2-Methyl-2-phenylthio-2-butanone (3c): ^1H NMR ($CDCl_3$) δ=1.05 (dd, 6H, J=7 Hz, 3 Hz), 1.04 (d, 3H, J=7 Hz), 2.7—3.2 (m, 1H), 3.85 (q, 1H, J=7 Hz), 7.0—7.7 (m, 5H); IR (neat) 2970, 1708, 1438, 1010 cm^{-1}; Anal. ($C_{12}H_{16}OS$) C, H.

1-Phenyl-1-(phenylthio)butane (3h): ^1H NMR ($CDCl_3$) δ=0.85 (t, 3H, J=6 Hz), 1.0—1.6 (m, 2H), 1.7—2.1 (m, 2H), 4.10 (t, 1H, J=7 Hz), 6.9—7.3 (m, 10H); IR (neat) 3060, 3030, 2960, 1480, 1453, 1438, 1050 cm^{-1}; Anal.($C_{16}H_{18}S$) C, H.

4,4-Ethylenedioxy-1-phenyl-1-(phenylthio)pentane (3i): ^1H NMR ($CDCl_3$) δ=1.30 (s, 3H), 1.5—2.3 (m, 4H), 3.7—3.9 (m, 4H), 4.10 (t, 1H, J=7 Hz), 7.0—7.5 (m, 10H); IR (neat) 2940, 1455, 1440, 1365 cm^{-1}; Anal.($C_{19}H_{22}O_2S$) C, H.

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