Conversion of Amides to *S*-Alkyl and *S*-Aryl Thioesters via Nitrosoamides and Nitroamides

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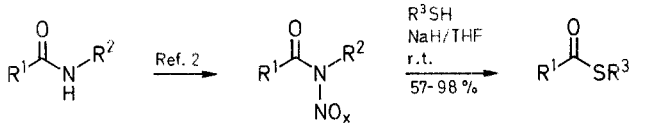
Thiolates react at room temperature with nitrosoamides and, even more rapidly, with nitroamides to afford good yields of *S*-alkyl and *S*-aryl thioesters; by-products arising from *N*-to-*S* transnitrosations and transnitrations are practically not observed.

It is known that *S*-alkyl, *S*-aryl, and *S*-heteroaryl thioesters offer advantages over the corresponding esters as far as certain reactions are concerned. Amides and peptides, for instance, can be obtained under quite mild conditions from thioesters and amines.[1] We considered that the reverse transformation (i.e., to convert amides into thioesters) could take place under smooth conditions as well. A simple way, not reported before to our knowledge, is presented in the following scheme. Nitrosoamides could afford thioesters plus diazohydroxides (or diazoalkanes), while nitroamides would yield thioesters plus nitroamines. Since the relative ease of preparation of these nitrosoamides and nitroamides has been commented on elsewhere in connection with other work,[2] attention is focused here on the second step of the amide-to-thioester transformations.



1a-c **2a-c** x = 1, **3a-c** x = 2 **4a-f**

2 and 3	R^1	R^2	4	R^1	R^3
a	Ph	Me	**a**	Ph	Et
b	n-C_8H_{17}	Me	**b**	n-C_8H_{17}	Et
c	n-C_8H_{17}	Bu	**c**	Ph	t-Bu
			d	n-C_8H_{17}	t-Bu
			e	Ph	Ph
			f	n-C_8H_{17}	Ph

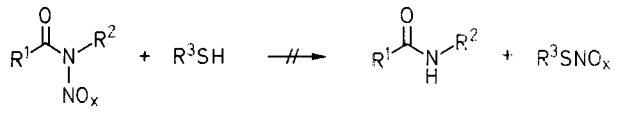
Part of our interest lay on applying such a transformation in protein semisynthesis: after the cleavage of selectively nitrosated peptide bonds,[3] the terminal thioester function would be readily converted into a new peptide bond or to another function. However, we envisaged that, taking into account the affinity of thiols for nitrogen oxides and nitrogen oxoacids, transnitrosation (and perhaps also transnitration) according to the following equation would compete with the desired attack to the carbonyl carbon atom. Furthermore both thionitrites and thionitrates are generally unstable: thionitrites decompose

Table. Reaction of Nitrosoamides **2a–c** and Nitroamides **3a–c** with Thiolates to Form *S*-Alkyl and *S*-Aryl Thioesters **4a–f**

Substrates	Thiolate	React. Time (min)	Product	Yield (%)	mp (°C) or bp (°C)/Torr	Molecular Formula[a] or Lit. mp or bp	IR ν(cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J(Hz)	^{13}C-NMR ($CDCl_3$) δ
2a	Na^+EtS^-	20	**4a**	95	75/0.2	128–130/12[6]	1670	1.30 (t, 3H, J = 7); 3.08 (q, 2H, J = 7); 7.3–8.1 (m, 5H)	14.8, 23.4, 127.1, 128.3, 128.5, 133.2, 137.3, 192.0
2a	Na^+t-BuS^-	20	**4c**	90	87/0.5	86/0.8[7]	1665	2.58 (s, 9H); 7.42 (m, 3H); 7.92 (m, 2H)	30.0, 48.1, 126.9, 128.4, 132.9, 138.3, 192.8
2a	Na^+PhS^-	20	**4e**	94[b]	59–60	54.5–55.5[8]	1685	7.2–7.6 (m, 8H); 7.8–8.1 (m, 2H)	127.3, 127.4, 128.7, 129.2, 129.5, 133.6, 135.1, 136.6, 190.2
2b	Na^+EtS^-	20	**4b**	95	81/0.3	$C_{11}H_{22}OS$ (202.3)	1690	0.92 (m, 3H); 1.30 (m, 15H); 2.58 (t, 2H, J = 7); 2.94 (q, 2H, J = 7)	14.1, 14.8, 22.6, 23.2, 25.7, 29.0, 29.1, 29.2, 31.8, 44.1, 199.5
2b	Na^+t-BuS^-	30	**4d**	83	91/0.3	$C_{13}H_{26}OS$ (230.6)	1690	0.90 (br t, 3H); 1.1–1.8 (m, 12H); 1.45 (s, 9H); 2.47 (t, 2H, J = 6.5)	28.9, 29.1, 29.2, 29.8, 31.8, 44.6, 47.7, 200.5
2b	Na^+PhS^-	30	**4f**	88[b]	154/0.4	$C_{15}H_{22}OS$ (250.4)	1705	0.92 (br t, 3H); 1.28 (m, 12H); 2.63 (t, 2H, J = 7); 7.37 (s, 5H)	14.1, 22.6, 25.6, 29.0, 29.1, 29.2, 31.8, 43.7, 128.0, 129.1, 129.2, 134.5, 197.6
2c	Na^+EtS^-	20	**4b**	95					
2c	Na^+t-BuS^-	30	**4d**	57[c]					
2c	Na^+PhS^-	30	**4f**	80[d]					
3a	Na^+EtS^-	< 2	**4a**	97					
3a	Na^+t-BuS^-	< 2	**4c**	97					
3a	Na^+PhS^-	< 2	**4e**	98					
3b	Na^+EtS^-	< 2	**4b**	95					
3b	Na^+t-BuS^-	< 2	**4d**	83					
3b	Na^+PhS^-	< 2	**4f**	90					
3c	Na^+EtS^-	< 2	**4b**	97					
3c	Na^+t-BuS^-	2	**4d**	73					
3c	Na^+PhS^-	2	**4f**	87					

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.3.
[b] Methyl phenyl sulfide was obtained in similar yields.
[c] Nonanoic acid was recovered in 40% yield.
[d] A 91% yield of butyl phenyl sulfide was also obtained.

to give R^3SSR^3 and NO,[4] while thionitrates may also be involved in nitrosation reactions.[5] In spite of these expectations, we have not detected in practice significant amounts of disulfides or related products nor of starting amides, a clean attack to CO being usually observed.



First of all, the direct reaction of nitrosoamides **2a–c** and of nitroamides **3a–c** with thiols was attempted, but no reaction was observed. Addition of an equivalent amount of triethylamine was beneficial, since starting from nitrosoamide **2a** thiol esters **4a, 4c,** and **4e** were obtained in 80–90% yields after several hours at room temperature; the problem was that only a 20% conversion was achieved from **2b**, *tert*-butyl hydrosulfide, and triethylamine after 3 days, and furthermore, that **2c** did not react at all with *tert*-butyl hydrosulfide and triethylamine after 4 days. Even though the yields were systematically higher, similar facts were observed with the nitroamides.

Thus, we turned our attention to the reactivity of nitrosoamides and nitroamides with thiolates. The results are summarized in the Table. As shown, good yields of **4** were obtained in few minutes, no matter whether the thiol was branched or aromatic. Although not included in the Table, reaction of **2** and **3** with these thiolates could be accomplished at 0 °C in a few min as well.

Nitroamides react faster than nitrosoamides under the same conditions. As seen in the Table, an instantaneous reaction was clearly produced even in the reaction of **3c** with sodium *tert*-butyl sulfide, to afford **4d** in 73% isolated yield. Moreover, when in independent experiments performed at dilute concentrations ($1.5 \cdot 10^{-4}$ M) we treated **3a** and **2a** with an excess of benzyltrimethylammonium benzenethiolate, **3a** reacted completely within 1 min, whereas **2a** required almost 48 h under the same conditions.

In summary, amide bonds, after either nitrosation or nitration in the cold, may be readily cleaved by thiolates at room temperature or at 0 °C to afford thiol esters as the major products.

S-Alkyl and S-Aryl Thioesters 4; General Procedure:
Nitrosoamide **2** or nitroamide **3** (2 mmol) is added to a stirred suspension arising from thiol (4 mmol) plus NaH (3 mmol) in anhydrous THF (ca. 10 mL) at room temperature in the presence of 4 Å molecular sieves. The color changes quickly, instantaneously in the case of **3**. The final mixture is concentrated carefully, and the residue partitioned in the cold between CH_2Cl_2 (50 mL) and 5% aq. Na_2CO_3 (10 mL). The organic layers are collected, dried (Na_2SO_4), and evaporated. The residues are analyzed by ^{1}H-NMR before being purified by chromatography through a small column of silica gel with CH_2Cl_2 as eluent.

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