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In Situ Reagents For Thionation Of Amides, Peptides And Lactams

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Abstract: *An in situ reagent* **1A** *for thionation of amides, peptides and lactams is prepared from phosphorus decasulfide/sodium carbonate (1:1 ratio) in THF at 25°C.*

Thioamides[1] and thiopeptides[2] are valuable synthetic intermediates. Also the Lawesson's[3] and Belleau's[4] reagents are highly convenient for thionation in general. In addition, *in situ* reagents prepared from phosphorus pentasulfide and pyridine[5], triethylamine[6], n-butyllithium[7] or sodium bicarbonate[8,9] are more accessible but perform a thionation under heterogeneous[5,7], basic[5,6] or heating[5,7,8] conditions. The *in situ* reagent sodium bicarbonate/phosphorus pentasulfide (6:1 ratio) described by Scheeren[8] involves formation of nucleophilic thiophosphate groups[10] thus thionating ketones but also dimethylformamide[8] at 40°C. In consideration that non negatively charged phosphorus atoms would be more reactive for thionation of

nucleophilic amides, we reduced the ratio of sodium carbonate/phosphorus pentasulfide to give a more electrophilic *in situ* reagent. We found indeed this modification to be a valuable one since a more reactive *in situ* reagent is obtained also being soluble both in THF and in water allowing an easy work-up procedure.

The reaction between phosphorus decasulfide and sodium carbonate[8] in a 1:1 ratio in tetrahydrofuran (Scheme I) affords after 10-20 minutes at 25°C a homogeneous solution of **1A**. Stability of **1A**[11] depends on the cation : $Na^+ >> K^+ > Cs^+ >> Li^+$. A plausible empirical formula $(P_4S_{10}O)^{2-}Na_2^{2+}$ shows both electrophilic and

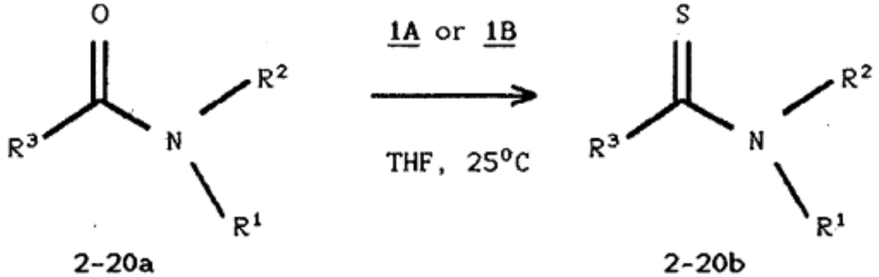
SCHEME I

$$P_4S_{10} + Na_2CO_3 \xrightarrow[-CO_2]{THF} (P_4S_{10}O)^{2-}Na_2^{2+}$$

1A

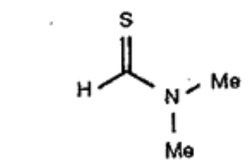
$$\underline{1A} \xrightarrow[15-20^{\circ}C]{2\ CF_3SO_3Me} \underline{1B} \quad (+\ 2\ CF_3SO_3^-\ Na^+)$$

SCHEME II

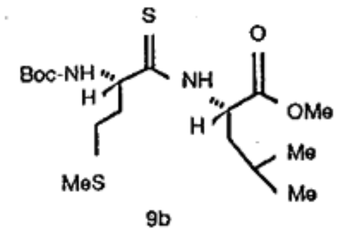


2-20a 2-20b

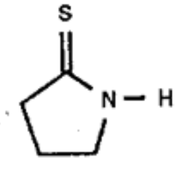
ionic[10] character of **1A**. The easy access to **1A** is complemented by an easy work-up since the ionic groups[11] allow a solubilization of **1A** in aqueous solutions. The increased reactivity of **1A** was proved[8] since thiodimethylformamide **2b** was formed rapidly at 25°C (5 min) and also at -20°C (91%)[8] (scheme II). The reagent **1A** thionated amide derivatives of t-Boc amino acids **3-6a** and dipeptides **7-8a** (Table I). These results show that thionation with **1A** is dependent upon steric hindrance of peptides. The complete formation of **7b** (81%) was however achieved at 50°C. Thionation of benzamides **11-13a** with **1A** afforded good yields of thiobenzamides **11-13b** (>90%). The sterically hindered diamide **14a** was converted to mono and dithionated products **14b** (43%) and **15b**[12] (12%). Many lactams **16-20a** were also converted by **1A** to thiolactams **16-20b** in good yields (81-88%). This method is superior to the reported formation of **19b** (30%)[7] and **20b** (37%)[7]. Also with reagent **1A**, thioacridone **21b** (96%) was easily obtained[13]. Better yields of thioamide **6b** were obtained with a 2:1 (25% **6b**) and 3:1 (33% **6b**) ratio of phosphorus pentasulfide/sodium carbonate, but the reagent was stable[10] for 20 minutes as a 3:1 ratio. These results allowed to thionate lactams **16,19-20a** using less reagent **1A** (5:3 ratio). Then we reasoned that methylation of ionic groups would increase the electrophilic character and reactivity of **1A**. Thus a



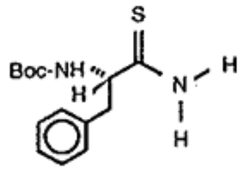
2b



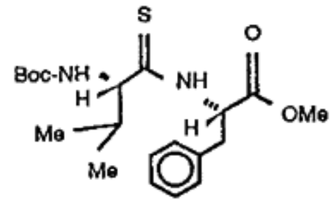
9b



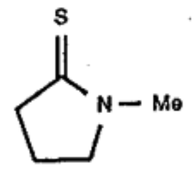
16b



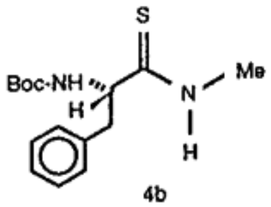
3b



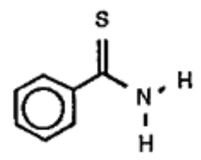
10b



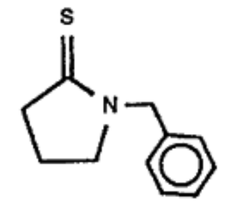
17b



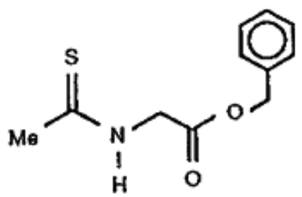
4b



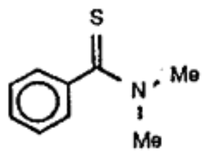
11b



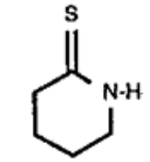
18b



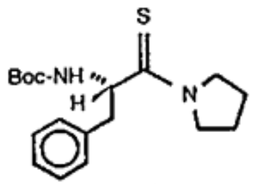
5b



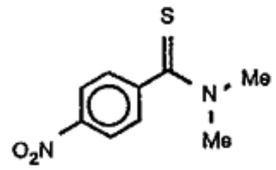
12b



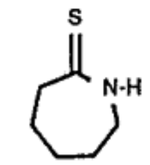
19b



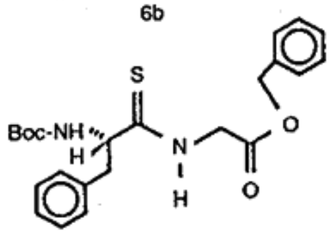
6b



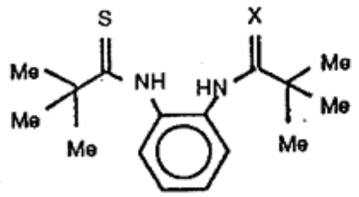
13b



20b

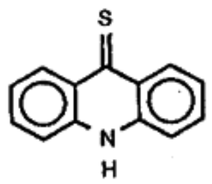


7b

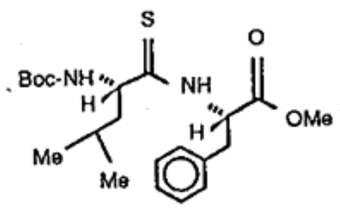


14b (X=O)

15b (X=S)



21b



8b

Table I. Thionation with reagents 1A and 1B

Product	Experimental conditions: reagent	Temperature, °C	time, h	Yield, [a] %
2b	1.2 **1A**	25	0.1	89
	1.2 **1A**	-20	18	91
3b	1.3 **1A**	0	8	80
4b	1.3 **1A**	25	5	78
5b	1.2 **1A**	0	8	76
	1.2 **1A**	25	2.5	80
6b	1.5 **1A**	25	1 or 24	19
	1.5 **1A**[b]	25	2	25
	1.5 **1A**[c]	25	0.3	33
	2 **1A**	50	4	41
	2 **1B**	25	8	72
7b	1.3 **1A**	25	6	28
	2 **1A**	50	4	81
	1.3 **1B**	25	4	84
8b	1.6 **1A**	25	6	30
	1.6 **1B**	25	2	75
9b	1.6 **1B**	25	2	72
10b	2.5 **1B**	25	10	28
11b	1.3 **1A**	25	2	90

(continued)

Table Continued

12b	1.5	**1A**	25	4	90
13b	1.5	**1A**	25	4	91
14b/	4	**1A**	25	10	43 / 12
15b	4	**1A**	50	4	51 / 23
	2.9	**1B**	25	10	1 / 80
16b	1.2	**1A**	25	2	88
	0.8	**1A**[d]	25	2	85
17b	1.3	**1A**	25	3	84
18b	1.5	**1A**	25	3	82
19b	1.2	**1A**	25	2	85
	0.8	**1A**[d]	25	2	81
20b	1.2	**1A**	25	2	84
	0.8	**1A**[d]	25	2	81
21b	1.3	**1A**	25	2	96

[a]Isolated from flash chromatography [b]2:1 ratio of phosphorus pentasulfide and sodium carbonate [c]3:1 ratio [d]5:3 ratio

reaction of **1A** with methyltrifluoromethanesulfonate at 15-20°C (Scheme I) gave a homogeneous *in situ* reagent assigned as **1B**. Reagent **1B** converted rapidly at 25°C amide **7a** to thioamide **7b** (84%) and **6a** to **6b** (72%). Furthermore the dithioamide **15b**[12] (80%) was obtained at 25°C using **1B**. The thiodipeptides **8-9b** were then

prepared in good yields (72-75%) except for the sterically hindered thiodipeptide **10b** (27%). An attempt to characterize **1A** and **1B** by ^{31}P NMR (15% THF-d_8/ THF) showed that several species were formed since two different complex spectrum (25-120 ppm) were obtained, analogous to similar study[7].

In summary, *in situ* reagents **1A** and **1B** are easy to prepare and useful for thionation of amides, peptides, lactams and an acridone at 25°C.

Experimental Section

Tetrahydrofuran was distilled from sodium/benzophenone prior to use. P_4S_{10} from BDH or Aldrich was used for the reactions. ^1H NMR spectra were recorded on a Bruker WH-400 spectrometer in $CDCl_3$/ 0.1% $(Me)_4Si$. Mass spectra (HRMS) were recorded on a Kratos MS50TCTA spectrometer at the Université de Montréal.

General Procedure 1: Reagent (1A). In a flask fixed with a gas outlet, P_4S_{10} (2.0 g, 4.5 mmol) and Na_2CO_3 (0.47 g, 4.5 mmol) are added to THF (30 mL). The mixture is stirred vigorously for 10-20 min and the amide is added. After completion of the thionation, a 10 % aqueous solution[14] of Na_3PO_4 (20 mL), AcOEt (15 mL) and hexanes (15 mL) are respectively added. The aqueous layer is washed with AcOEt (1X 10 mL). The organic layer is dried with $MgSO_4$ then filtered on a silica gel pad. The crude thioamide can be further purified by chromatography on silica gel.

General Procedure 2: Reagent (1B)[10]. To the above solution of **1A** at 15-20°C is added quickly (1/2 min) CF_3SO_3Me (0.95 mL, 8.5 mmol). After 2-3 min, the amide is added and the solution is filtered on frited glass under argon (0.12-0.1 M of **1B** after dilution). The work-up is identical to procedure 1.

Thiodimethylformamide (2b). Chromatography (AcOEt): ^1H NMR δ 3.32, 3.35 (2 s, 6 H, CH_3), 9.24 (s, 1 H, HC=S); IR 2985, 1525, 1395, 1130 cm^{-1}; MH^+ = 90.

t-Boc-L-phenylalanyl Thioamide (3b). Chromatography (AcOEt/hex 1:2): mp 104-105°C (AcOEt/hex -20°C); $[\alpha]^{20}_D$ +44.0° (c 1, $CHCl_3$); ^1H NMR δ 1.40 (s, 9 H, CH_3), 3.16 (s, 2 H, β CH_2), 4.61 (q, J = 7.8 Hz, 1 H, α CH), 4.92 (bs, 1 H, NH), 7.30 (m, 7 H, Ar, NH_2): IR 3425-3100, 2980, 1695, 1493, 1165 cm^{-1}; exact mass calcd for $C_{14}H_{20}N_2O_2S$ 280.1246, found 280.1249.

t-Boc-L-phenylalanyl Thioamide (4b). Chromatography (AcOEt/hex 1:2): mp 112-113°C (AcOEt/hex); $[\alpha]^{20}_D$ +63.8° (c 1, $CHCl_3$); ^1H NMR δ 1.40 (s, 9 H, CH_3), 3.01, 3.14 (2 m, 2 H, β CH_2), 4.55 (q, J = 7.6 Hz, 1 H, α CH), 5.42 (bs, 1 H, NH Boc), 7.28 (m, 5 H, Ar), 7.63 (bs, 1 H, NHC=S); IR 3495, 2935, 1690, 1495, 1165 cm^{-1}; exact mass calcd for $C_{15}H_{22}N_2O_2S$ 294.1402, found 294.1416.

Thioacetamide (5b). Chromatography (AcOEt): mp 86-87°C (AcOEt/hex); ^1H NMR δ 2.61 (s, 3 H, CH_3), 4.44 (d, J = 4.4 Hz, 2 H, CH_2), 5.24 (s, 2 H, CH_2O), 7.37 (s, 5 H, Ar), 7.66 (bs, 1 H, NH); IR 3475, 1760, 1365, 1188 cm^{-1}; exact mass calcd for $C_{11}H_{13}NO_2S$ 223.0667, found 223.0666.

t-Boc-L-phenylalanyl Thioamide (6b). Chromatography (AcOEt/hex 1:3): $[\alpha]^{20}_D$ +95.1° (c 1, $CHCl_3$); ^1H NMR δ 1.39 (s, 9 H, CH_3), 1.80 (m, 4 H, CH_2 cycl), 2.08 (m, 2 H, β CH_2), 2.60 (m, 1 H, CH_2 cycl), 3.61 (m, 3 H, CH_2 cycl), 4.88 (q , J = 7.4 Hz, 1 H, α CH), 5.82 (bs, 1 H, NH), 7.28 (m, 5 H, Ar); IR 2960, 1685, 1475, 1165 cm^{-1}; exact mass calcd for $C_{18}H_{26}N_2O_2S$ 334.1715, found 334.1735.

Thiodipeptide t-Boc-Pheψ[CSNH]Gly-OBn (7b). Chromatography (AcOEt): mp 108-109°C (AcOEt/hex); $[\alpha]^{20}_D$ +27.8° (c 1, $CHCl_3$); ^1H NMR δ 1.39 (s, 9 H, CH_3), 2.04 (s, 2 H, β CH_2), 4.25 (m, 2 H, CH_2N), 4.62 (m, 1 H, α CH), 5.17 (s, 2 H, CH_2O), 5.23 (m, 1 H, NH Boc), 7.36 (m, 10 H, Ar), 7.94 (s 1 H, NH); IR 2980, 1730, 1690, 1485, 1160 cm^{-1}; exact mass calcd for $C_{23}H_{28}N_2O_4S$ 428.1771, found 428.1747.

Thiodipeptide t-Boc-Leuψ[CSNH]Phe-OMe (8b). Chromatography (AcOEt/hex 1:3): $[\alpha]^{20}_D$ +77.1° (c 1, $CHCl_3$); ^1H NMR δ 0.94 (d, J = 6.8 Hz, 6 H, CH_3), 1.43 (s, 9 H, CH_3), 1.6-1.64 (m, 2 H, β CH_2 Leu), 1.76 (m, 1 H, CH Leu), 3.22, 3.41 (2m, 2 H, β CH_2 Phe), 3.74 (s, 3 H, CH_3O), 4.34 (m, 1 H, α CH Leu), 5.03 (m, 1 H, NH Boc), 5.35 (m, 1 H, α CH Phe), 7.09, 7.27 (2m, 5 H, Ar), 8.18 (s, 1 H, NHC=S); IR 2970, 1750, 1720, 1510, 1175 cm^{-1}; exact mass calcd for $C_{21}H_{32}N_2O_4S$ 408.2085, found 408.2093.

Thiodipeptide t-Boc-Metψ[CSNH]Leu-OMe (9b). Chromatography (AcOEt/hex 1:3): $[\alpha]^{20}_D$ -13.4° (c 1, $CHCl_3$); ^1H NMR δ 0.95 (m, 6 H, CH_3 Leu), 1.44 (s, 9 H, CH_3 Boc), 1.75 (m, 3 H, CH-CH_2 Leu), 2.08 (m, 2 H, β CH_2), 2.13 (s, 3 H, CH_3S), 2.62 (m, 2 H, CH_2S), 3.75 (s, 3 H, CH_3O), 4.58 (m, 1 H, α CH Leu), 5.11 (m, 1 H, α CH Met), 5.46 (m, 1 H, NH Boc), 8.16 (bs, 1 H, NHC=S); IR 2980, 1750, 1715, 1505, 1180 cm^{-1}; exact mass calcd for $C_{17}H_{32}N_2O_4S_2$ 392.1805, found 392.1797.

Thiodipeptide t-Boc-Valψ[CSNH]Phe-OMe (10b). Chromatography (AcOEt/hex 1:5): $[\alpha]^{20}_D$ +99.2° (c 1, $CHCl_3$); ^1H NMR δ 0.92 (d, J = 6.5 Hz, 6 H, CH_3), 1.45 (s, 9 H, CH_3), 2.27 (m, 1 H, β CH Val), 3.25, 3.35 (2m, 2 H, β CH_2 Phe), 3.73 (s, 3 H, CH_3O), 4.02 (m, 1 H, α CH Val), 5.19 (m, 1 H, NH Boc), 5.39 (m, 1 H, α CH Phe), 7.09, 7.26 (2 m, 5 H, Ar), 8.02 (s, 1 H, NHC=S); IR 2980, 1750, 1710, 1510, 1180 cm^{-1}; exact mass calcd for $C_{20}H_{30}N_2O_4S$ 394.1928, found 394.1910.

Thiobenzamide (11b). Chromatography (AcOEt/CH_2Cl_2/hex 1:1:1): mp 88-89°C (AcOEt/hex); ^1H NMR δ 6.02, 7.15 (2 bs, 2 H, NH_2), 7.53, 7.88 (2 m, 5 H, Ar); IR 3460, 2985, 1590, 1320 cm^{-1}, exact mass calcd for C_7H_7NS 137.0300, found 137.0294.

N,N-Dimethylthiobenzamide (12b). Chromatography (AcOEt/hex 2:1): mp 67-68°C (neat -20°C); ^1H NMR δ 3.16, 3.60 (2 s, 6 H, 2 CH_3), 7.33 (m, 5 H, Ar); IR 3000, 1530, 1410, 1310 cm^{-1}; exact mass calcd for $C_9H_{11}NS$ 165.0613, found 165.0612.

N,N-Dimethyl-p-nitro-thiobenzamide (13b). Chromatography (AcOEt/CH_2Cl_2 2:1): mp 141-142°C (CH_2Cl_2/hex); ^1H NMR δ 3.17, 3.61 (2 s, 6 H, 2 CH_3), 7.46, 8.24 (2 m, 4 H, Ar); IR 2990, 1545, 1370, 860 cm^{-1}; exact mass calcd for $C_9H_{10}N_2O_2S$ 210.0464, found 210.0475.

o-Thioanilide (14b) and o-Dithioanilide (15b). Chromatography (AcOEt/hex 1:6 then 1:4). For **14b:** mp 172-174°C (CCl_4/hex -20°C); ^1H NMR δ 1.29 (s, 9 H, CH_3), 1.46 (s, 9 H, CH_3), 7.26 (m, 2 H, Ar), 7.47 (m, 2 H, Ar), 7.80 (s, 1 H, NHC=O), 9.40 (s, 1 H, NHC=S); IR 2960, 1640, 1510, 1480 cm^{-1}; exact mass calcd for $C_{16}H_{24}N_2OS$ 292.1611, found 292.1580. For **15b:** mp 191-192°C (CCl_4/hex -20°C); ^1H NMR δ 1.44 (s, 18 H, CH_3), 7.26, 7.44 (2 m, 4 H, Ar), 9.07 (s, 2 H, NH); IR 2980, 1515, 1485, 1140 cm^{-1}; exact mass calcd for $C_{16}H_{24}N_2S_2$ 308.1383, found 308.1395.

2-Thiopyrrolidone (16b). Chromatography (AcOEt): mp 109-110°C (CH_2Cl_2/hex); ^1H NMR δ 2.23 (m, 2 H, CH_2), 2.92 (t, J = 8.0 Hz, 2 H, CH_2), 3.68 (t, J = 7.4 Hz, 2 H, CH_2), 8.61 (bs, 1 H, NH); IR 2980, 1505, 1285, 1110 cm^{-1}; exact mass calcd for C_4H_7NS 101.0299, found 101.0303.

N-Methyl-2-thiopyrrolidone (17b). Chromatography (AcOEt): ^1H NMR δ 2.08 (q, J = 7.5 Hz, 2 H, CH_2), 3.05 (t, J = 7.9 Hz, 2 H, CH_2), 3.27 (s, 3 H, CH_3), 3.75 (t, J = 7.3 Hz, 2 H, CH_2N); IR 2960, 1550, 1350, 1335 cm^{-1}; exact mass calcd for C_5H_9NS 115.0457, found 115.0460.

N-Benzyl-2-thiopyrrolidone (18b). Chromatography (AcOEt/hex 1:1): mp 70-71°C (neat -20°C); ^1H NMR δ 2.02 (q, J = 7.5 Hz, 2 H, CH_2), 3.10 (t, J = 7.8 Hz, 2 H, CH_2), 3.59 (t, J = 7.3 Hz, 2 H, CH_2), 4.99 (s, 2 H, CH_2N), 7.33 (m, 5 H, Ar); IR 2960, 1505, 1450, 1305 cm^{-1}; exact mass calcd for $C_{11}H_{13}NS$ 192.0769, found 192.0800.

2-Thiopiperidone (19b). Chromatography (AcOEt/hex 1:1 then 1:0): mp 92-93°C (CH_2Cl_2/hex); ^1H NMR δ 1.79 (m, 4 H, CH_2), 2.89 (t, J = 6.4 Hz, 2 H, CH_2), 3.36 (m, 2 H, CH_2N), 9.11 (m, 1 H, NH); IR 2940, 1535, 1345, 1110 cm^{-1}; exact mass calcd for C_5H_9NS 115.0457, found 115.0461.

ϵ-Thiocaprolactam (20b). Chromatography (AcOEt/hex 1:1): mp 103-104°C (CH_2Cl_2/hex); ^1H NMR δ 1.73 (m, 6 H, CH_2), 3.02 (m, 2 H, CH_2), 3.40 (m, 2 H, CH_2N), 8.77 (bs, 1 H, NH); IR 2920, 1520, 1110 cm^{-1}; exact mass calcd for $C_6H_{11}NS$ 129.0613, found 129.0624.

Thioacridone (21b). mp 260-262°C (AcOEt/hex); ^1H NMR δ (DMSO-d_6) δ 7.41, 7.69, 7.85, 8.88 (4 m, 8 H, Ar), 9.58 (bs, 1 H, NH); IR (nujol) 3020, 1620, 1588, 1220 cm^{-1}; exact mass calcd for $C_{13}H_9NS$ 211.0462, found 211.0457.

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(10) Reaction of P_4S_{10} with $NaHCO_3$[8] or n-BuLi[7] involves phosphorus-sulfide bond breaking and formation of ionic thiophosphate groups.

(11) Reagents **1A** and **1B** slowly transform[7,8] due to solid particles or upon heating, to non reactive gelatinous mass. Filtration of the solution is better if heating of **1A** or use of the less stable **1B** is considered. Preparation of **1B** on large scale is highly risky.

(12) Compound **15b** (85%) was also prepared using Belleau's reagent[4] (3 eq ; 30 h at 40°C).

(13) Thionation of acridones with P_4S_{10} in HMPT at 110°C: Claude, S.; Lehn, J.M.; Vigneron, J.P., *Tetrahedron Lett.*, **1989**, 30, 941-944.

(14) 2 equivalents of NaOH (2M in water) can be used.