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THE REACTION OF NITROACETAMIDES WITH THIONATION REAGENTS SYNTHESIS OF MONO- AND DITHIO- OXALIC ACID DIAMIDES

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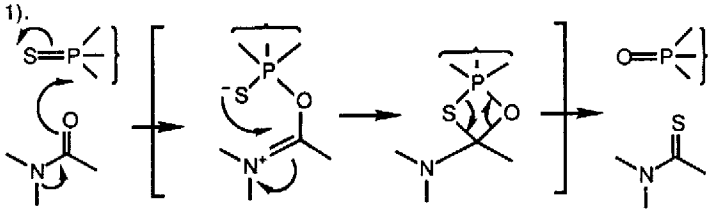
Summary : Nitroacetamides, $R^1(R^2)N.CO.CH_2NO_2$, react with phosphorus sulphide (P_4S_{10}) or 2,4-bis(4-methoxyphenyl)-1,2-dithiadiphosphetane-2,4-disulphide, Lawesson's reagent, to give amide-thioamides, $R^1(R^2)N.CO.CS.NH2$.

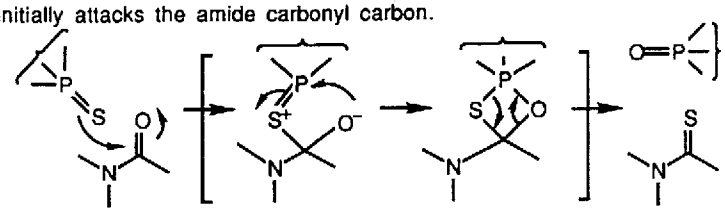
Methods for the direct conversion of amides to thioamides centre on the use of phosphorus sulphides and derivatives, particularly P_4S_{10}[1]. The process can be visualised[2] as involving carbonyl oxygen attack at phosphorus, the collapse of the ylid intermediate to a four-membered Wittig-like species which then re-opens in the opposite sense (Scheme 1).

Scheme 1

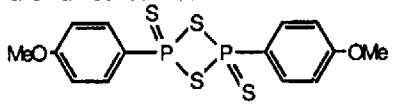


In an alternative view[3] (Scheme 2), lent some support by the recognition of the catalytic effect of added triethylamine or bicarbonate, or organolithiums[4] on amide-thionation with P_4S_{10}, a nucleophilic phosphorus-sulphur species initially attacks the amide carbonyl carbon.

Scheme 2



2,4-Bis(4-methoxyphenyl)-1,2-dithiadiphosphetane-2,4-disulphide,1[5], generally called Lawesson's reagent (LR)[6,7], has been developed as a superior reagent for the conversion of carbonyl, including amide carbonyl, to thiocarbonyl. Dedimerisation of LR to generate an ylid **2**, then as in Scheme 2, has been proposed on ^{31}P NMR evidence[8] for a small concentration of the zwitterionic 'monomer' **2**.



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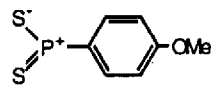

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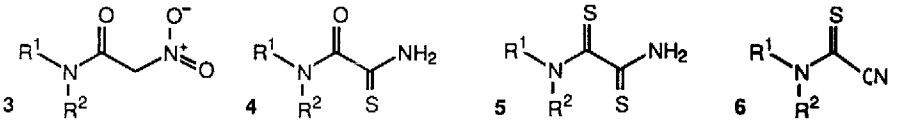


3 4 5 6

a: R^1=H, R^2=Me; b: R^1=R^2=H; c: R^1=R^2=Me; d: R^1=H, R^2=Ph; e: R^1=H, R^2=4-$MeOC_6H_4$; f: R^1=H, R^2=4-ClC_6H_4; g: R^1+R^2=$(CH_2)_4$; h: R^1+R^2=$(CH_2)_5$

Table

Starting amide	Products[a] (m.p. (°C)) (% yields) 4	5	6	7	Conditions	Time (h); temp (°C)
3a	122-23	100subl.	-	oil		
	60	5	-	-	b	80; 0.25
	23	17	-	-	c	40; 16
	60	5	-	2	d	100; 0.25
	30	25	8	-	e	40; 2
3b	174-76	90-100	-	-		
	32	14	-	-	b	80; 0.5
	21	14	-	-	c	80; 0.2
3c	105-110		56-60	oil		
	-	14	25	-	b	100; 0.25
	-	4	-	-	c	80; 2
	16	12	-	1	d	80; 0.5
3d	174-76	83-86	-	-		
	68	8	-	-	b	100; 0.25
	44	13	-	-	c	80; 3
3e	179-83	-	-	-		
	40	-	-	-	b	110; 0.2
3f	200	-	-	-		
	62	-	-	-	b	110; 0.5
3g	157-59	175	oil	65-85		
	-	21	16	-	b	100; 0.25
	-	17	8	-	c	100; 0.25
	12	7	6	5	d	100; 0.25
3h	96-100	oil	oil	78-88		
	7	12	34[f]	trace	d	100; 0.75

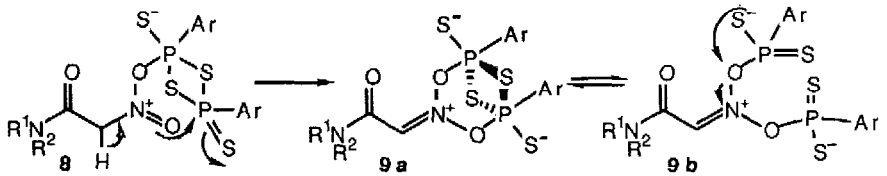
(a) All new compounds gave satisfactory elemental analyses or accurate mass-measured molecular ions (for oils); compounds already reported had comparable m.ps.
(b) The nitro-acetamide **3** was heated with a stirred slurry of Lawesson's reagent (1.1 mol equiv) in anhydrous toluene at the temperature indicated until all starting material had been consumed (tlc). After cooling, the solvent was evaporated and products isolated by chromatography over silica eluting with CH_2Cl_2-EtOAc.
(c) The nitroacetamide **3** was heated with a stirred slurry of P_4S_{10} (1.5 mol equiv) in 1,4-dioxane at the temperature indicated until all starting material had been consumed (tlc), then as in (b).
(d) As in (b) except that after evaporation of toluene, the total was dissolved in warm methanol and the solution kept for 15 min before re-evaporation and chromatographic isolation.
(e) As in (c) but with ultrasonication.
(f) $(C_5H_{10})N.CO.CN$.

We suggest, particularly for the less electrophilic, amides, that the alternative view, (Scheme 1), and perhaps involving attack on LR itself, is more likely. Support for this view can be taken from analogies with the efficient conversion of tertiary amides into thioamides using N,N-diethylthiocarbamoyl chloride, considered[9] to involve amide carbonyl in an initial nucleophilic attack on the reagent, and to the conversions of sulphoxides[10a] and sulphimines[10b] to sulphides, and of sulphines to thiones[10c], for which nucleophilic attack at phosphorus and the intermediacy of four-membered intermediates was also suggested[10a].

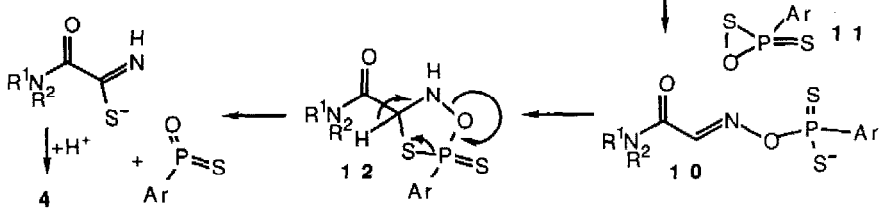
In the hope of converting N-methylnitroacetamide **3a** into its thioamide analogue[11], and reassured by reports[6,12] that (aromatic) nitro groups survive LR thionation conditions, we treated **3a** with LR in hot toluene; after 15 min, no starting material remained, and amide-thioamide **4a**, and a lesser quantity of dithiodiamide **5a** had been produced. Exposure of **3a** to P_4S_{10} in hot dioxan produced the same two products. Examination of a range of nitroacetamides (Table) with LR and P_4S_{10}, showed that the formation of thioamides under these conditions is a general process.

To rationalise formation of the three product types, **4**, **5**, and **6**, one may firstly deduce, since no nitrothioacetamides were obtained, that dithiodiamides **5** are formed from amide-thioamides **4** by the recognised route, and we showed that **4d** was efficiently transformed into **5d** by extended treatment with LR. Secondly, we suggest that the thioacyl cyanides **6** are formed simply by loss of hydrogen sulphide from a thioamide precursor.

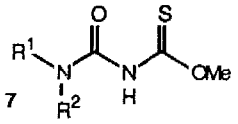
Considering the primary transformation, CH_2NO_2 into $C{:}S.NH_2$, it might seem relevant to consider the Meyer variation of the Nef reaction[13] which transforms CH_2NO_2 into CO.OH. However, it is known that this proceeds[14] *via* an intermediate still carrying an oxygen on nitrogen (nitrile oxides have been imputed, and hydroxamic acids can be isolated), the present instance differs in that both oxygens have been removed from nitrogen while sulfur at thione oxidation level is transfered to the methylene carbon. As regards the removal of oxygen, a similar mechanistic problem was posed by the transformations reported by Barton, of nitro-compounds into oximes with CS_2/Et_3N[15] or $P(Bu)_3(SPh)_2$[16a] and of oximes to imines[16b] using $P(Bu)_3(SPh)_2$, and our suggestion derives in part from rationalisations presented[15,16].



Scheme 3



We favour a view of the interaction of LR with nitroacetamides in which the phosphorus is attacked by nucleophilic nitro-oxygen, possibly *via* intramolecular delivery following initial reaction at amide oxygen[17]. We suggest (Scheme 3) that an initial adduct, **8**, by proton loss and interaction of the second nitro-group oxygen with phosphorus, possibly (as shown) the second phosphorus of the reagent, would produce **9a/b**. Reduction at nitrogen (arrows on **9b**) to**10**, and a species, **11**, loss of sulphur from which one would anticipate to be very easy, completing the redox cycle. Thioamide formation would proceed from **10** *via* intramolecular delivery of sulphur (-> **12**), then fragmentation, and protonation.



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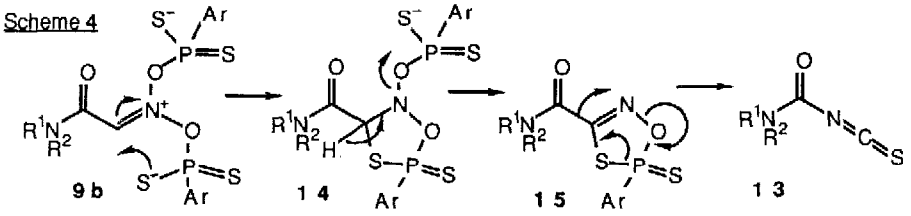
Initially observed adventitiously from the use of methanol in chromatography, we isolated, *via* treatment of LR product mixtures with methanol, small quantities of methoxythiocarbonylureas, **7**. Clearly such products require a precursor isothiocyanate, **13**, and Scheme 4 shows how these could arise from **9** (Scheme 3) : cyclisation to **14**, 1,2-elimination giving **15**, and a Beckmann-like 1,2-shift (arrows on **15**) would produce the isothiocyanate **13**.

Scheme 4



9b **14** **15** **13**

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