Reaction of Phosphorus Pentasulfide with Organolithiums. An *In Situ* Reagent for the Preparation of Thiolactams

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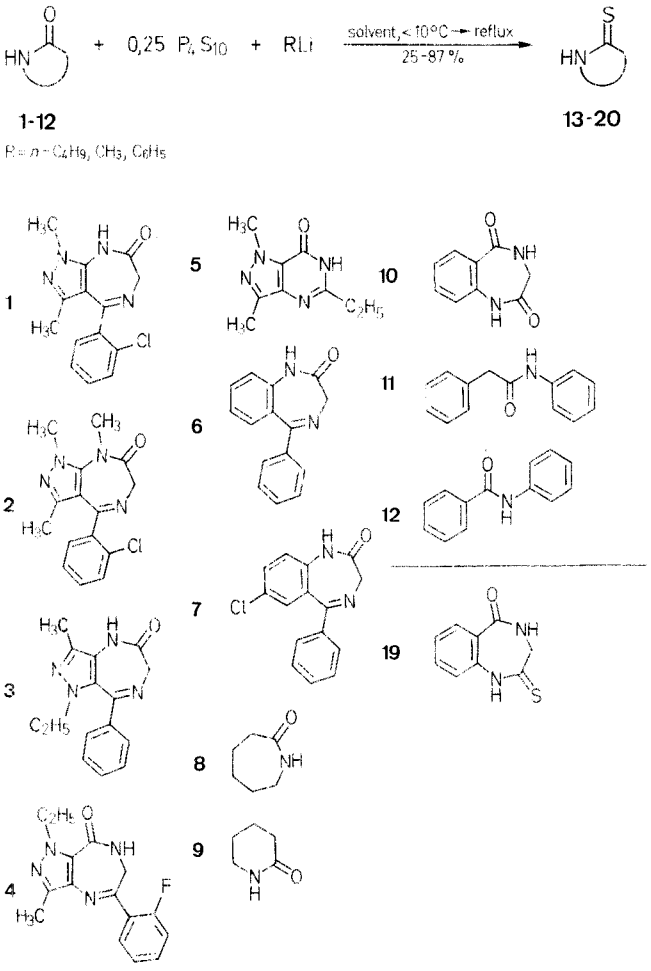
Phosphorus pentasulfide reacts under mild conditions with four equivalents of *n*-butyllithium, methyllithium or phenyllithium giving solutions in tetrahydrofuran. The new reagents *in situ* convert lactams to thiolactams and show significant selectivity in the type of reactive lactams.

Thioamides and thiolactams have many applications in organic synthesis.[1,2] One of these is in the preparation of amidines which have been utilized in the synthesis of heterocyclic fused diazepine ring systems.[3,4] The latter exhibit desirable anxiolytic activity with minimal sedative side-effects. For the large scale preparation of 4-(2-chlorophenyl)-6,8-dihydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]-diazepine-7(1*H*)-thione (entry 1 in the Table) we investigated a number of reagents.[5,6] Reaction of the lactam in entry 1 with phosphorus pentasulfide in pyridine at 80° gave impure thiolactam which required purification by chromatography. When we treated this lactam with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) in pyridine (50°C, 3 hours), a 90% yield of the desired product was obtained. Alternatively, the analogous thionation reagent described by Belleau[7] may be used. The main drawbacks of these reagents are the high temperature required for their large scale preparation and the disposal of the toxic hydrogen sulfide gas produced. There was a need for an, easy to prepare, *in situ* reagent to effect the desired transformation. We assumed that an organolithium reagent would be a source of stronger nucleophilic carbon (compared to anisole used to prepare Lawesson's reagent) to break the phosphorus-sulfur bond in phosphorus pentasulfide and this would generate a suitable *in situ* reagent which may be useful in achieving the oxygen to sulfur exchange in amides and lactams. We found this to occur and the results are presented in this communication. Steliou and Mrani[8] have also reported an *in situ* reagent obtained by treating bis(tricyclohexyltin)sulfide with boron trichloride which yields thiolactams from lactams.

Addition of four equivalents of a 2.6 molar solution of *n*-butyllithium solution in hexane to a stirred, cooled (5–10°C) slurry of phosphorus pentasulfide in tetrahydrofuran under a nitrogen atmosphere caused an exothermic reaction as most of phosphorus pentasulfide readily dissolved. The reaction was completed by stirring for an additional hour at room temperature giving a clear yellow solution. When a 1.6 molar solution in hexane was used, a pale yellow oil separated from the mixture.[9] A similar reagent complex was obtained when commercial solutions of methyllithium in ether or phenyllithium in cyclohexane/ether were used. Each of the reagent complexes was stable if heated at reflux.

To the *n*-butyllithium/phosphorus pentasulfide (4:1) reagent complex in tetrahydrofuran was added the lactam 1, and the mixture heated to reflux. Within half an hour at reflux, a solution formed and a yellow solid precipitated. The mixture was refluxed for 16 hours, cooled to 5°, and the product collected, washed with cold tetrahydrofuran, and dried to afford an 81% yield of the desired thiolactam (entry 1, Table). The yield did not improve when the amount of reagent was increased by 50%. Somewhat lower yields were obtained in this reaction when methyllithium or phenyllithium complexes with phosphorus



pentasulfide were used (entry 2, 3). To determine the scope of *n*-butyllithium/phosphorus pentasulfide reagent a number of substrates were treated with it. Significant selectivity was observed. The results obtained are summarized in the table. The products were isolated as described above or by aqueous work-up. Generally, good yields (65–87%) were obtained for the thiolactams in entries 1, 5, 8, and 9. If the nitrogen of the lactam was alkylated (entry 4) there was no reaction and all starting material was recovered. Most significantly, if the carbonyl group of the lactam was conjugated with the aromatic ring, no reaction occurred (entry 6 and 7). This is, presumably, due to the less electrophilic nature of the carbonyl group. When both conjugated and unconjugated lactam functions were present in the same substrate, only the unconjugated mono thiolactam was obtained (entry 12). The reagent offers selectivity in this regard. Nonrigid lactams (entry 10 and 11) gave modest yield of product. Pyricones (2- or 4-) did not react even in hexamethylphosphortriamide which enhanced solubility of these substrates. In case of thioamides, a 20% yield was obtained in entry 13 but again no reaction was observed when the amide carbonyl group was conjugated with the aromatic ring (entry 14). Lawesson's reagent is reported[20] to give excellent yields of thioamides from both these substrates.

Attempts were made to isolate and characterize the product of the reaction between phosphorus pentasulfide and organolithiums. Removal of the solvent under high vacuum at ambient temperature produced colorless viscous gums. After triturating with ether, an insoluble, largely inorganic, amorphous solid was filtered off. However, when the remaining soluble portions were reconstituted in tetrahydrofuran, the lactam to thiolactam transformation failed to take place. The nature of the reagent

Table. Preparation of Thiolactams[a]

Entry	Substrate[b]	Product No.	Yield[c] (%)	m.p. (°C)[c]	Appearance	Literature m.p. (°C)
1	**1**[14,d]	**13**	81	231–232 (dec.)	Yellow powder	170–220 (dec.)[4]
2		**13**	77	232–233 (dec.)		
3		**13**	62	233–234 (dec.)		
4	**2**[14,e]	No Reaction	0	–		
5	**3**[15]	**14**	65	280 (dec.)	Pale yellow powder	280–281 (dec.)[23]
6	**4**[15]	No Reaction	0	–		
7	**5**[16]	No Reaction	0	–		
8	**6**[17]	**15**	65	236–238	Off-white powder	236–237[18]
9	**7**[19]	**16**	87	233–234	Off-white powder	244–246[19,f]
10	**8**	**17**	37	103	Pale yellow solid	106[20]
11	**9**	**18**	30	87–93	Pale yellow needles	95–96[21]
12	**10**[22,g]	**19**	25	277–283	Pale yellow crystals	–[h]
13	**11**	**20**	20	85	–	87[20]
14	**12**	No Reaction	0	–		

[a] All reactions were carried out using the reagent, $P_4S_{10} \cdot 4n\text{-}C_4H_9Li$ in THF/hexane at reflux for 16 h, except in entries 2 and 3. For each P_4S_{10} molecule, 3.8–4.0 equivalents of substrate was used except in entry 12, where the substrate amount was 2.0 equivalents. Reagent used in the case of entry 2: $P_4S_{10} \cdot 4CH_3Li$ in THF/ether; entry 3: $P_4S_{10} \cdot 4C_6H_5Li$ in THF/ether/cyclohexane.

[b] The preparation of each substrate, not commercially available, is described in the reference cited.

[c] Yields and melting points are of unrecrystallized materials which gave satisfactory microanalyses, IR, ^{1}H-NMR and MS data.

[d] Reaction with Lawesson's reagent in pyridine gave 13 in 90% yield; m.p. 232–233 (dec.).

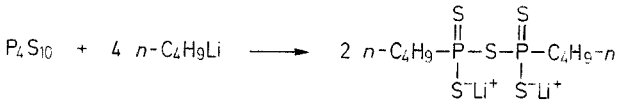
[e] Reaction with Lawesson's reagent in HMPT gave the corresponding thiolactam in 10% yield.

[f] Literature m.p. is of material recrystallized from DMF-CH_3OH.

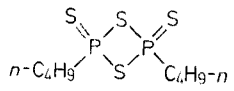
[g] Reaction with Lawesson's reagent in HMPT gave **19** in 50% yield.

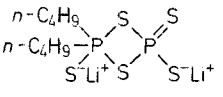
[h] New compound, recrystallized from DMF-CH_3OH.
$C_9H_8N_2OS$ (192.2) calc. C 56.23 H 4.19 N 14.57 S 16.68; found 56.18 4.25 14.58 16.72
IR (KBr): ν = 3159, 1780 cm^{-1}.
^{1}H-NMR (DMSO-d_6/TMS): δ = 3.96 (d, 2H, J = 6.0 Hz); 7.23–7.81 (m, 4H); 8.83 (t, 1H, J = 6.0 Hz); 12.38 ppm (s, 1H).

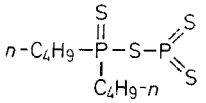
complex changed substantially during removal of the solvent. A ^{31}P-NMR of an undisturbed phosphorus pentasulfide/*n*-butyllithium (1:4) solution in tetrahydrofuran-d_8 was obtained from which it was not possible to assign a structure to the reagent. The ^{31}P-NMR of the Lawesson's reagent was similarly complex.[10,11] It is likely that a mixture of components exists in complexation with the solvent. The reaction of Grignard reagents with phosphorus pentasulfide has been investigated,[12,13] and the major product was isolated after hydrolysis. Based on analogy the following reagent species may be postulated:



However, species such as:







may be present in the mixture which would account for the complex ^{31}P-NMR spectrum.

4-(2-Chlorophenyl)-6,8-dihydro-1,3-dimethylpyrazolo[3,4-*e*][1,4]-diazepin-7(1*H*)-thione (16); Typical Procedure:

A slurry of phosphorus pentasulfide (9.3 g, 0.021 mol) in dry tetrahydrofuran (170 ml) is stirred and cooled to 5 °C under a nitrogen atmosphere. *n*-Butyllithium solution in hexane (50.4 ml, 15.01% w/w, d = 0.7, 0.084 mol) is carefully transferred to a dry addition funnel and added slowly to the slurry of phosphorus pentasulfide keeping the temperature below 10 °C. The cooling bath is removed and the mixture stirred for 1 h at room temperature. All phosphorus pentasulfide dissolves and a pale oil separates from the mixture. To the stirred mixture is added 4-(2-chlorophenyl)-6,8-dihydro-1,3-dimethylpyrazolo [3,4-*e*][1,4]-diazepin-7(1*H*)-one (**1**; 23 g, 0.08 mol) in one portion and the mixture is heated to reflux. An orange red solution forms at 50 °C and a yellow solid precipitates after 30 min at reflux. After 16 h, the mixture is cooled to 5 °C and the product collected, washed with cold tetrahydrofuran, and dried to afford the thiolactam **13**; yield: 19.8 g (81%); m.p. 231–232 °C (Table).

$C_{14}H_{13}ClN_4S$ (304.8) calc. C 55.17 H 4.30 N 18.38 S 10.52; found 55.21 4.50 18.20 10.27

Alternatively, if the product does not precipitate from the reaction mixture (as in entry 9), the solvent is removed and the residue triturated with water. The product is collected and dried. The product may also be isolated by extraction of the aqueous mixture with chloroform. The chloroform solution is dried, solvent evaporated, and the residue triturated with cyclohexane to yield crystalline thiolactams.

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2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide in THF + THF-d_8: δ = 79.12 (96.67); 76.46 (36.18); 71.85 (168.96); 71.59 (173.9); 20.37 (12.78); 20.32 (13.1); 16.81 (151.5); 10.10 (41.17); 9.82 ppm (40.35).
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