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Novel Protocol for Synthesis of *O,O*-Dialkyl Monothiophospharic Acid Sodium Salt

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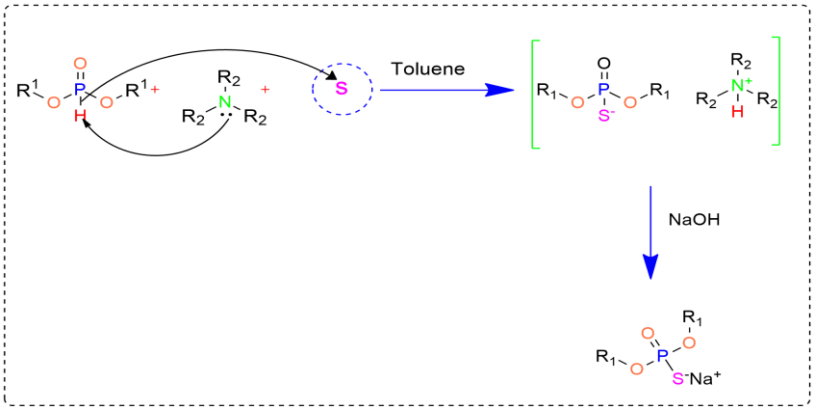
Preparation of *O,O*-dialkyl monothiophospharic acid sodium salt (DMP-SNa) by addition of sulphur selectively on phosphorous using organic base to form a salt of *O,O*-dialkyl monothiophospharic acid trialkyl amine salt which is soluble in the non-polar organic solvent and treated with alkali to form *O,O*-dialkyl monothiophospharic acid sodium salt (DAP-SNa). Trialkylamine becomes free and remains in the nonpolar solvents can be recycled. This synthesis method is effluent free.

Graphical abstract



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1. Introduction

O,O-Dialkyl monothiophospharic acid sodium Salt [DAP-SNa] [1] is an important raw material in chemical industries. It is used to prepare azamethiphos [2,3], which is an organothiophosphate insecticide used as veterinary drug in Atlantic salmon fish [4,5] farming to control parasite and is also used for control of flies and cockroaches [6]. *O,O*-Dialkyl monothiophospharic acid sodium salt is good sulphur nucleophile [7] and reacting with alkyl and benzyl halide very easily. S-alkyl organo phosphorus compounds act as an agricultural, horticultural, bactericidal, and insecticidal agents.

As per literature survey, DAP-SNa synthesis methods are reported as a) dimethyl phosphite treated with sodium methoxide and sulfur [1], b) rearrangement of *S*-(2-aminoethyl) thiophosphates to *N*-(2-mercaptoethyl)phosphoramidates in dichloromethane [8], c) dibenzoyl disulfide reaction with dimethylphosphite in presence of *N*-ethyl-*N,N*-diisopropylamine in 1,2-dichloro-ethane at 20 °C [9], d) dimethylphosphite reaction with sulfur in presence of sodium methoxide [10], e) cyanophos treated with sodium hydroxide in 1,4-dioxane; water at 25 °C [11,12], f) diethylphosphite reaction with sulfur in presence of sodium methoxide in inert atmosphere [13], g) diphenylphosphite reaction with sulfur; triethylamine in diethyl ether for 3h Reflux [14], h) diphenylphosphite reaction with sulfur; triethylamine in diethyl ether for 3h; reflux [15]. Main drawback of all reported synthesis method is lower yield and generation of toxic reaction waste. Generally negative charge on sulfur migrating on oxygen at higher temperature leads formation of DAPS-ONa salt instead of DAP-SNa. In present invention developed effluent free and high yield synthesis method for preparation of *O,O*-dialkyl monothiophospharic acid sodium salt. Here DAP-SNa formation ensured by *S*-alkylation (Scheme 3) and

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achieved 80% target compound, rest of 20% product is Michaelis-Arbuzov rearrangement product.

2. Material and Methods

All chemicals were purchased from commercial source and used without further purification. Physical constants of synthesized compounds were determined by using open point capillary, using paraffin oil. The progress of reaction and purity of compound were determined by High performance liquid chromatogram (Agilent HPLC).^{1}H NMR Spectroscopy were recorded in DMSO-d6 and tetramethyl silane (TMS) as an internal standard using Bruker 400-MHz instrument.

2.1 General procedure for preparation of compound 6a-e

Compound **2** (1.01 eq) and compound **3** (1.02 eq) are taken in toluene (334 mL) further mixed at 25 to 30 °C. Prepared a solution of compounds **1a-e** (1.0 mol) and toluene (133 mL) in a separate beaker and added into above reaction mass drop wise. The above reaction mass was stirred at 35-39° C for about 60 min. Added 20% NaOH (0.99 eq) into clear reaction mass at 35-39 °Separated the layers and washed aqueous layer with toluene. Concentrated aqueous solution at 35 to 38 °C using 10 torr vacuum obtained white solid of compound **6a-e**.

2.2 General procedure for preparation of compound 4f-j

Compounds **2f-j** (1.01 eq) and compound **3** (1.02 eq) are taken in toluene (334 mL) further mixed at 25 to 30 °C. Prepared a solution of compound **1** (1.0 mol) and toluene (133 mL) in a separate beaker and added into above reaction mass drop wise. The above reaction mass stirred at 35-39 °C for about 60 min. Distilled out toluene at 35 to 40°C using vacuum. Obtained clear colourless oil of compounds **4f-j**.

2.3 General procedure for preparation of compound 8a-g

Compound **7a-g** (1.0 mol) treated with of compound **6** (1.2 eq) in methanol (650 mL). Stir reaction mass at 25 to 30 °C over a period of 20 h to obtain compound **8a-g**. Compounds **8a-e** isolated by extraction with dichloromethane and compounds **8f-g** isolated by filtration.

***O,O*-Dimethyl monothiophospharic acid sodium salt (6a):** White solid, yield 98%, LC purity 98%, Melting point is above 300 °C, ^{1}H NMR (400Hz, DMSO-d6) 3.326(6H, d, 19Hz).

***O,O*-dimethyl monothiophospharic acid, *N,N*-dimethyl benzylamine (4f):** Clear colourless liquid, ^{1}H NMR (400Hz DMSO-d6) 2.504 (6H, S), 3.359 (6H, d, 12Hz), 4.23 (2H, S), 7.469 (5H, m), 10.85 (NH, S).

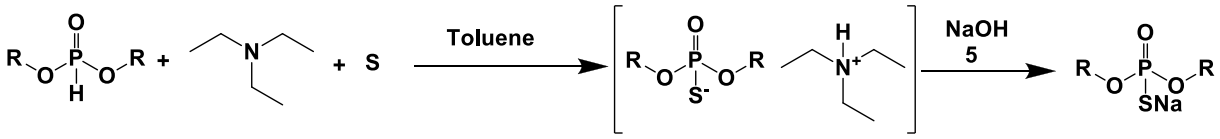
S- [(6-chloro-2-xo [1,3] oxazolo [4,5, b] pyridine-3(2H)-yl) methyl] *O,O*-dimethyl phosphorothioate (8f): White solid, M.P 89 to 91°C. ^{1}H NMR (400Hz DMSO-d6) 8.29 (1H, d , 4Hz), 8.12 (1H, d , 4Hz), 5.26 (1H, S) 5.22 (1H, S), 3.833 (6H, d, 12Hz).

S- [(2-oxo [1,3] oxazolo [4,5, b] pyridine -3(2H)-yl) methyl] *O, O*-dimethyl phosphorothioate (8g): White solid, yield is 68% with LC purity 98%. ^{1}H NMR (400Hz DMSO-d6). 3.647 (6H, d, 12.8Hz), 5.235 (2H, d, 15.2 Hz), 7.237(1H, d, 13.2 Hz), 7.782 (1H, d, 9.2 Hz), 8.186 (1H, d, 6.4Hz).

S-benzyl *O,O*-dimethyl phosphorothioate (8a): Colourless liquid, Yield 60%,^{1}H NMR (400Hz DMSO-d6). 3.601 (6H, d, 11.6Hz), 4.016 (2H, d) 7.26 (5H, m).

3. Results and Discussion

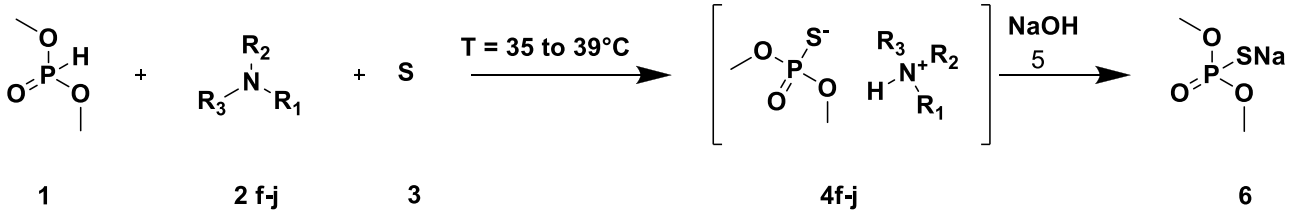
Selective addition of sulphur on phosphorus done by preparing organic salt of dialkyl phosphite using tertiary amine (Scheme 2, **4a-j**) in non-polar solvent like toluene. After complete formation of organic salt of dimethyl phosphite, unreacted sulphur removed by simple filtration and clear filtrate is treated with NaOH to form at 35 to 39 °C. Tertiary amine remains in toluene and can be recycle in the process. Aqueous layer concentrated to obtain white solid of *O,O*-Dialkyl monothiophospharic acid sodium salt which is used for alkylation reaction. Product confirm by ^{1}H NMR.



	R
1a	CH_3
1b	CH_3CH_2
1c	$CH_3CH_2CH_2$
1d	CH_3CHCH_3
1e	$CH_2CH_2CH_2CH_3$

Scheme 1. Synthesis of compounds **4a-e** and **6a-e.**

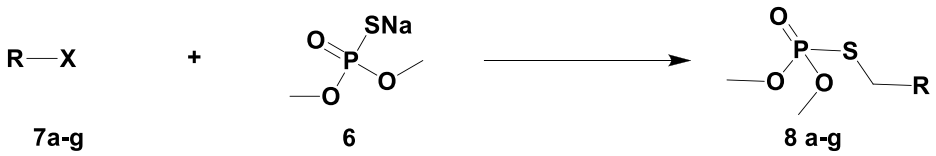
Reaction performed by using compound 1 (1.0 mol), compounds **2f-j** (1.01 mol), compound 3 (1.02 mol), and toluene as per procedure given in 2.2 (Scheme 2), gives compounds **4f-j**. Reaction time and yield summarized in Table 1. Main objective of synthesis of compound **4f-j** is to ensure selective addition of sulphur on phosphorus.



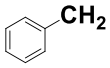
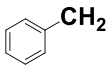
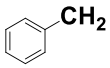
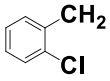
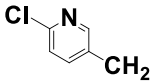
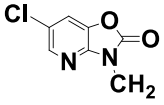
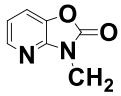
1 2 f-j 3 4f-j 6

	R_1	R_2	R_3
2f	CH_3	CH_3	$C_6H_5CH_2$
2g	CH_3CH_2	CH_3CHCH_3	CH_3CHCH_3
2h	CH_3	CH_3	C_6H_5
2i	CH_3CH_2	CH_3CH_2	C_6H_5
2j	C_6H_5	CH_3CH_2	CH_3CH_2

Scheme 2. Synthesis of compounds **4f-j** and **6**.



7a-g 6 8 a-g

	R	X
7a		Cl
7b		Br
7c		I
7d		Cl
7e		Cl
7f		Cl
7g		Cl

Scheme 3. One pot synthesis of compound **8a-g**.

Table 1. Preparation of compound **4f-j**.

Sr. No	Compound	Organic base	Time(h)	% Yield
1	4f	*N,N*-dimethyl benzyl amine	2	100
2	4g	*N*-ethyl-*N,N*-di-	2	100
3	4h	isopropyl amine.	2	100
4	4i	*N,N*-dimethyl aniline.	2	94
5	4j	*N,N*-Diethyl aniline. Triethylamine.	2	94

Preliminary basis, reaction performed by using compounds**1a-e** (1.0 mol) using compound 2 (1.01 mol), compound **3** (1.02 mol), compound **5** (0.99 mol) and toluene (334 mL) by applying same reaction conditions as it applied in general reaction procedure 2.1. Reaction time and yield summarized in Table 2.

For optimization of reaction temperature, the reaction had done by using dimethyl phosphite (1 mol), sulphur (1.02 mol), toluene (334 mL), *N,N*-dimethyl benzyl amine (1.01 mol),

NaOH (0.99 mol) which gives the desired product. At higher temperatures product is not stable leads lower yield. At 15 to 20 °C rate of reaction is slow and reaction mass remains turbid leads lower yield. At 35 to 40 °C reaction mass is clear homogeneous solution and obtained the desired yield.

Table 2. Reaction optimization for compounds **6a-e.**

Sr. No	Compound	Dialkyl phosphite	Time (h)	% Yield
1	6a	Dimethyl phosphite	2	98
2	6b	Diethyl phosphite	2	95
3	6c	Di-propyl phosphite	2	94
4	6d	Di-isopropyl phosphite	2	94
5	6e	Di-butyl phosphite	2	94

Table 3. Reaction optimization for temperature.

Sr. No	Temp (°C)	% Yield
1	15 to 20	85
2	25 to 30	90
3	35 to 40	98
4	40 to 45	80
5	55 to 60	55

For the selection of solvent for reaction, the reaction is done by using dimethyl phosphite (1 mol), sulphur (1.02 mol), and *N,N*-dimethyl benzyl amine (1.02 mol), NaOH (0.99 mol) and used different solvents (334 mL) as *per* procedure 2.1, which gives the desired product. Toluene and monochlorobenzene works well. Reaction time and yield summarized in Table 4.

Table 4. Reaction optimization for solvents.

Sr. No	Solvent for Alkali	Time (h)	Temp (°C)	% Yield
1	Toluene	2	35 to 40	100
2	Monochlorobenzene	2	35 to 40	100
3	Dichloromethane	2	35 to 40	90
4	0-Xylene	2	35 to 40	92
5	1,2-dichloroethane	2	35 to 40	90

For optimization of moles of *N,N*-dimethyl benzylamine, reaction done by using dimethyl phosphite (1.0 mol), sulphur (1.02 mol), toluene (334 mL) and moles of *N,N*-dimethyl benzylamine varies from 1.0 moles to 1.15 moles. Reaction time and yield summarized in Table 5.

Table 5. Reaction optimization for *N,N*-dimethyl benzylamine moles.

Sr. No	Moles	Temp(°C)	%Yield
1	1.15	35 to 40	95
2	1.10	35 to 40	95
3	1.05	35 to 40	95
4	1.02	35 to 40	98
5	1.0	35 to 40	98

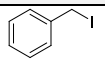
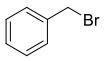
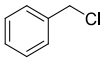
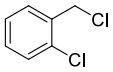
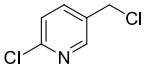
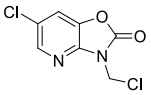
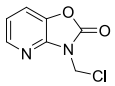
Conversion of organic salt to inorganic salt, organic layer treated with aqueous alkali. For optimization of alkali, reaction done by using dimethyl phosphite (1.0 mol), sulphur (1.02 mol), toluene (334 mL), *N, N*-dimethyl benzylamine (1.0 mol). Reaction mass heated at 35 to 40 °C. Reaction mass treated with different alkali (1.0 mol), obtain respective metal salt. Reaction time and yield data summarized in Table 6.

Negative charge on sulphur delocalised on oxygen leads formation of DMPS-ONa salt instead of DMP-SNa salt. Though structure is confirmed by ^{1}H-NMR it is necessary to ensure formation of DMP-SNa. We treated compound **6** with aromatic benzyl halide (7a-g) as per procedure 2.3, obtained compound **8a-g** structure confirmed by ^{1}H-NMR. Reaction time and yield summarized in Table 7.

Table 6. Reaction optimization for alkali.

Sr. No	Alkali	Moles of Alkali	Solvent for Alkali	%Yield
1	NaOH	1.0	Methanol	98
2	KOH	1.0	Methanol	98
3	NaOH	1.0	Water	98
4	KOH	1.0	Water	98
5	Na_2CO_3	0.5	Water	95
6	K_2CO_3	0.5	Water	95

Table 7. *S*-alkylation reaction aromatic benzyl halide.

Sr. No	Compound	Compound RX	Time (h)	%Yield
1	8a		6	80
2	8b		10	80
3	8c		10	80
4	8d		10	75
5	8e		16	72
6	8f		20	75
7	8g		20	75

4. Conclusions

We have demonstrated that totally eco-friendly, commercially viable and catalyst-free method, for the synthesis of *O,O*-dialkyl monothiophospharic acid sodium salt. Here trialkyl amine and solvent can be recover and recycle in the process. There is no waste generation in the process. 45 to 50% solution in water is stable at room temperature. *O,O*-dialkyl monothiophospharic acid sodium salt isolated by distillation of water at 35 to 38 °C using vacuum. Sulphur successfully added on phosphorus. Due to greater selectivity yield is quantitative.

Author Contributions

Umesh Keru Patil: He performed reference work and all laboratory work. Dr. Kawade D.S.: He performed reference work and spectroscopic data analysis. Dr. S.R. Vaidya: She is research supervisor.

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