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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL PROPERTIES OF TRI-SCHIFF'S BASES CONTAINING CORE-PHOSPHOROTHIOATE MOIETY

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Abstract

In the present manuscript, the facile synthesis of tri-Schiff's bases, containing the core-thiophosphate moiety by using O,O,O-tris(4-formylphenyl) phosphorothioate, **3** and substituted anilines as a precursor has been reported. The key precursor **3** has been prepared under mild conditions in presence of $(C_4H_9)_4NBr$ as a phase transfer catalyst. All the synthesized compounds **(5a-5h)** were screened for their antibacterial and antifungal activities and were found to show good to excellent antibacterial and antifungal activities as compared to the standards.

Keywords: Tetrabutylammonium bromide, Thiophosphoryl chloride, O,O,O-tris(4-formylphenyl) phosphorothioates, tri-Schiff's base, antibacterial and antifungal activities.

INTRODUCTION

Phosphorus is known to play an important role in biological systems due to its involvement in the number of metabolic reactions, enzymatic processes, photosynthesis and nucleic acid helices and in several biochemical reactions concerned with the transport and storage of energy.[1-4] Organophosphorus compounds are well known as one of the most important groups of modern pesticides[5-7].These compounds have attracted much attention of the research community as these possess unique potential biological properties such as antifungal, antibacterial, antileukemic, antiparasitic, antiviral, anti-inflammatory, antitumoral, antihypertensive and antioxidant.[7-16] Moreover, in the recent research,some useful organophosphate esters have been reported[17-19] acting as a prodrug which inhibits influenza virus replication in human bronchial epithelial cells and influenza virus-induced expression of many inflammatory cytokines in a *PPARγ*-dependent (*peroxisome proliferator*-activated receptor gamma) manner[19] . Schiff's bases, firstly reported in 1864 by "Hugo Schiff"', are condensation products of primary amines and carbonyl compounds.[21] These are also called imines or azomethines owing to the inclusion of the characteristic –CH=N group in their structure. Among the organic reagents used in the research field the Schiff's bases possess excellent characteristics, structural similarities with natural biological substances, relatively simple methods of preparation and synthetic flexibility that enables the design of suitable structural properties.[21-22] Schiff's bases synthesized from aromatic aldehydes and aromatic amines exhibit a wide range of applications in various fields such as in biological, analytical, and inorganic chemistry.[23-26] These are basic units in certain dyes and liquid crystals also used in the synthesis of compounds containing carbon-nitrogen bonds. These compounds act as important

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intermediates in many enzymatic reactions involving the interaction of an enzyme with amino or a carbonyl group of substrate.[27] The Schiff's bases containing sulfur, nitrogen and oxygen are good chelating ligands, antimicrobial agents[28-29] and anti tubercular agents.[30] 2-Azetidinone(β-lactum), a Schiff's base derivative possesses consequential antifungal, antibacterial, anti tubercular[31]and antimalarial, anti-inflammatory, antiviral and antipyretic activities.[32-34] In the recent research,it has been observed that theSchiff bases and their complexes are good candidates as versatile compounds, used for a variety of industrial application in oxidation catalysisand had focused on employing metal-catalyzed oxidation of organic compounds.[35-36]

This work is a continuation of ongoing work in our research laboratory on the synthesis and characterization of organophosphorus compounds[37-40]. In the present investigation we are reporting synthesis of an intermediate namely O,O,O-tris(4-formylphenyl) phosphorothioate(trialdehyde,3), which is then subsequently reacted with the variety of substituted anilines in the presence of glacial acetic acid as a catalyst forming tri-Schiff's bases **(5a-5f)** with thiophosphate moiety at a core**.** All the synthesized tri-Schiff's bases **(5a-5f)** were screened for their antibacterial and antifungal activity.

Although numbers of reports are available indicating a synthesis of Schiff's bases in the last twenty years, synthesis of tri-Schiff bases **(5a-5f)** having thiophosphate moiety at its core and their activity is not reported yet. Thus this is the first time, to the best of our knowledge; we are reporting such a synthesis and their antimicrobial activities.

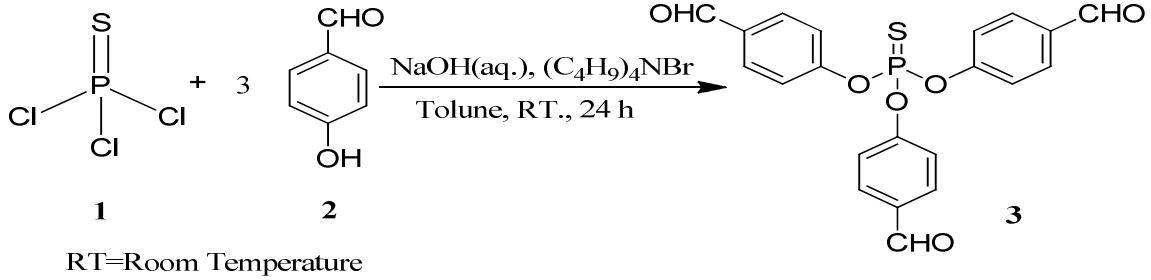
EXPERIMENTAL

Material and Methods

All the starting materials and reagents were purchased from commercial suppliers, Alfa Aesar, Merk Pvt. Ltd., Sd. Fine Chemicals Mumbai, Aldrich USA and used without further purification. Melting points were determined by open glass capillaries and may be uncorrected. The purity of compounds was checked by TLC. The IR spectra of all compounds were recorded in KBr on Shimadzu FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Advance 400MHz spectrometer using TMS as an internal standard. The ^{13}C spectra were recorded on EI-Shimadzu-GC-MS spectrometer.

General Procedure for the Synthesis of O,O,O-tris(4-formylphenyl) phosphorothioate (3)

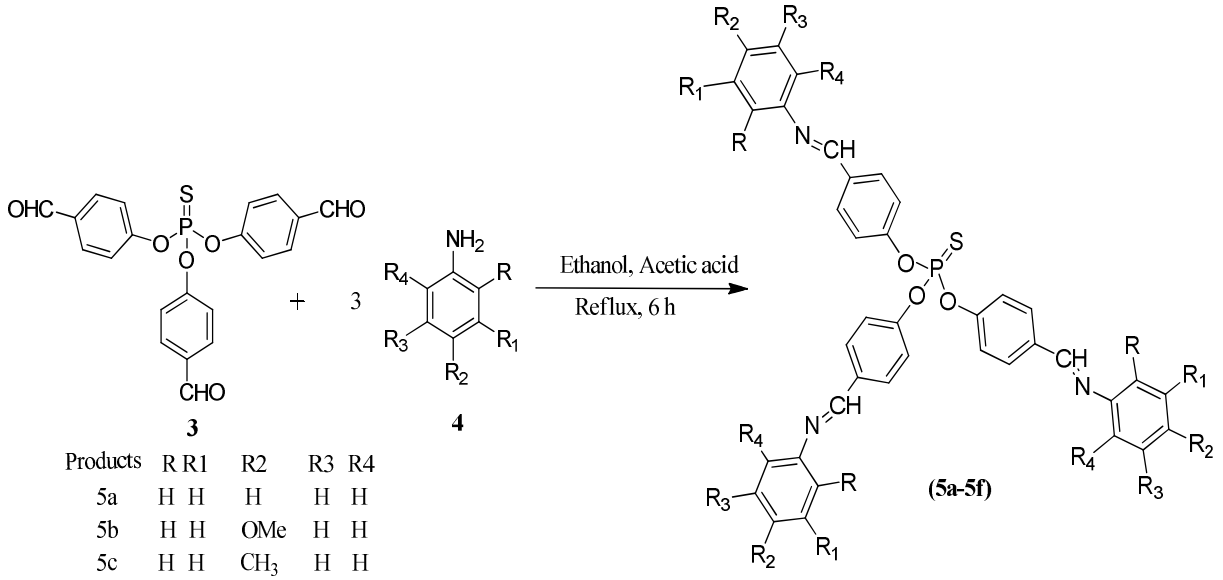
To a solution of thiophosphoryl chloride (1.69g, 10 mmol) and toluene (60 mL), TBAB $(C_4H_9)_4NBr$ (15 mg) was added and subjected to vigorous stirring. After five minutes sodium salt of *p*-hydroxy benzaldehyde (Benzaldehyde 3.66 g, NaOH 1.2 g in water 30 mL.) was added and continued stirring for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction the organic layer was separated and washed with 10% NaOH twice and then once with distilled water. The further organic layer was dried over anhydrous sodium sulphate, filtered and evaporated under vacuum to get the white crystalline product, which was further recrystallized in absolute ethanol.



Scheme-1: Synthesis of O,O,O-tris(4-formylphenyl) phosphorothioate, 3

General Procedure for the Synthesis of tri-Schiff Bases(5a–5f)

A mixture of O,O,O-tris(4-formylphenyl) phosphorothioates (1 mmol) and variously substituted anilines (3 mmol) dissolved in ethanol (25 mL), followed by a drop of glacial acetic acid and allowed to reflux for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled and the solution was evaporated under vacuum. The solid precipitated was recrystallized in acetonitrile.



Products	R	R1	R2	R3	R4
5a	H	H	H	H	H
5b	H	H	OMe	H	H
5c	H	H	CH_3	H	H
5d	H	H	COOH	H	H
5e	H	H	Cl	H	H
5f	H	NO_2	H	H	H

Scheme-2: Synthesis of Tri-Schiff bases (5a–5f)

Spectral Data of O,O,O-tris(4-formylphenyl) phosphorothioate (3)

White solid; m.p. (°C): 110-118, R_f Value: 0.28, Yield: 71%,IR (KBr)cm^{-1}: 756(P=S str.), 1156-1190(P-O-C(phenyl)-str), 3021(olefinic =C-H, Ar-C-H), 2739(aldehydic CH str.). ^{1}H-NMR ($CDCl_3$): δ 7.40-7.42(m, 6H, Ar- H), 7.94-7.96(d, J=8.00Hz, 6H, Ar-H), 10.14(s, 3H, CHO) ppm. ^{13}C-NMR ($CDCl_3$):δ 121.8, 134.26, 154.6, 190.5 ppm. ^{31}P-NMR ($CDCl_3$): δ 49.7 ppm. Defragmented EIMS-M/Z(relative abundance,%): 321.1(M^+,100).

Spectral Data of the tri- Schiff's Base Products (5a-5f)

Tris(4-{(phenylimino)methyl}phenyl) phosphorothioate (5a): White solid; m.p. (°C): 96-99, R_f Value: 0.80, Yield: 80%,IR (KBr) cm^{-1}: 760(P=S str.), 1160-1210(P-O-C- str). 1630(-C=N- str.) 3030(olefinic =C-H, Ar C-H). 2840(HC=N- str.). ^{1}H-NMR ($CDCl_3$): δ 7.23-7.45(m, 21H, Ar-H), 7.98-8.00(d, J=8.4Hz, 6H, Ar-H), 8.48(s, 3H, HC=N-) ppm. ^{13}C-NMR ($CDCl_3$)*: δ* 120.8, 121.6, 126.2, 129.25, 130.4, 134.1, 151.7, 152.6, and 158.7 ppm. ^{31}P-NMR ($DMSOd_6$): δ 51.6 ppm.

Tris(4-(4-methoxyphenylimino)methyl)phenyl) phosphorothioate (5b)

White solid; m.p. (°C): 163-167, R_f Value: 0..57, Yield: 91%,IR (KBr)cm^{-1}: 770(P=S str.), 1160-1210(P-O-C- str), 1620(-C=N- str.), 3020 (olefinic =C-H, Ar C-H), 2820(HC=N- str.). ^{1}H-NMR ($DMSOd_6$): δ 3.76(s, 9H, Ar-OCH3), 6.89-6.91(d, J=8.00Hz, 6H, Ar-H), 7.22-7.38(m, 12H, Ar-H), 7.96-7.98(d, J=8.00Hz, 6H, Ar-H), 8.55(s, 3H, HC=N) ppm.

Tris(4-(*p*-tolylimino)methyl)phenyl) phosphorothioate (5c)

White solid; m.p. (°C): 120-126, R_f Value: 0.73, Yield: 87%,IR (KBr)cm^{-1}: 790(P=S str.), 1150-1200(P-O-C-str), 1650(-C=N- str.), 3030 (olefin =C-H, Ar C-H), 2830(HC=N- str.). ^{1}H-NMR ($CDCl_3$): δ 2.40(s. 9H, Ar-CH3), 7.15-7.40 (m, 18H, Ar-H), 7.96-7.98(d, J=8.4Hz, 6H, Ar-H), 8.49 (s, 3H, HC=N) ppm. ^{13}C-NMR ($CDCl_3$): δ 77.3, 120.7, 121.5, 129.8, 130.2, 134.2, 136.0, 149.1, 152.5, 157.8 ppm. ^{31}P-NMR ($DMSOd_6$): δ 51.8 ppm.

Tris(4-(4-carboxyphenylimino)methyl)phenyl) phosphorothioate (5d)

White solid;m.p(°C): 172-174, R_f Value: 0.54, Yield: 70%,IR (KBr)cm^{-1}: 780(P=S str.), 1720(C=O), 1150-1210(P-O-C- str), 1650(-C=N- str.), 3030(olefinic =C-H, Ar C-H), 2820(HC=N- str.), 3520b (OH

str.). ^{1}H-NMR (DMSOd_6): δ 7.16-7.18(d, J=8.4Hz, 6H, Ar-H), δ= 7.35-7.42(m, 6H, Ar-H), 7.93-7.98(m, 12H, Ar-H), 8.48(s, 3H, HC=N), 9.95(s,3H, -COOH) ppm.

Tris(4-(4-chlorophenylimino)methyl)phenyl) phosphorothioate (5e)
White solid; m.p(°C): 130-134. R_f Value: 0.78, Yield: 82%, IR (KBr)cm^{-1}: 780(P=S str.), 1155-1200(P-O-C- str), 1620(-C=N- str.). 3040(olefinic =C-H, Ar C-H). 2880(HC=N- str.).^{1}H-NMR (DMSOd_6): δ 7.16-7.41(m,18H, Ar-H), 7.96-7.98(d, J=8.4Hz, 6H, Ar-H), 8.45(s. 3H, CH=N) ppm. ^{13}C-NMR (DMSOd_6): δ 121.6, 122.1, 129.3, 130.4, 131.7, 133.9, 150.1, 152.7 and 158.93 ppm, ^{31}P-NMR (DMSOd_6): δ 51.4 ppm.

Tris(4-(3-nitrophenylimino)methyl)phenyl) phosphorothioate (5f)
White solid; m.p(°C): 136-142. R_f Value: 0.60, Yield: 79%, IR (KBr)cm^{-1}: 780(P=S str.), 1000-1220 broad(P-O-C- str, C-O, C-N str), 1620(-C=N- str.). 3040(olefinic =C-H, Ar C-H). 2880(HC=N- str.). ^{1}H-NMR (DMSOd_6): δ 6.88-6.90(d, J=8.4Hz 6H, Ar-H), 7.21-7.39(m, 12H, Ar-H), 7.95-7.97(m, 6H, Ar-H), 8.53(s. 3H, HC=N) ppm.

RESULTS AND DISCUSSION

The intermediate O,O,O-tris(4-formylphenyl) phosphorothioate was prepared by stirring one equivalent of thiophosphoryl chloride and 3.2 equivalent of the sodium salt of *p*-hydroxy benzaldehyde in the presence of $(C_4H_9)_4NBr$ as a phase transfer catalyst and toluene as a solvent, at 25 °C temperature for 24 h. O,O,O-tris(4-formylphenyl) phosphorothioate was employed for the synthesis of tri-Schiff's base **(5a-5f),** by refluxing with various anilines, **4** in ethanol and glacial acetic acid as a catalyst for 6 h. afforded in good yield.

We have introduced here the use of $(C_4H_9)_4NBr$ as a phase transfer catalyst for the synthesis of O,O,O-tris(4-formylphenyl) phosphorothioate at mild conditions afforded 71% yield. Initially tri-Schiff's base **5a** was obtained in good yield, using the synthetic method outlined in Scheme-1. The formation of **5a** is confirmed by the IR spectrum of **5a** which has indicated the disappearance of aldehyde function and appearance of the HC=N function of tri-Schiff's bases. A further variety of tri-Schiff's bases **(5b-5f)** were synthesized by the similar procedure using an array of substituted anilines containing electron withdrawing and releasing substituent to account the effect of substituent on the yield of tri-Schiff's base. The electronic properties of substituents on anilines have a noticeable influence on the yield of transformation. Anilines with electron-donating (methoxy and methyl) substituent give high yields and that of electron-withdrawing (carboxyl and chlorine) substituent comparatively gives a low yield. Both intermediate, 3 and tri-Schiff bases **(5a-5f)** were purified by recrystallization method, saving the much more isolation time.

Intermediate, **3** and all the -Schiff bases **(5a-5f)** were recrystallized and analyzed for their confirmation using FT-IR and NMR (^{1}H, ^{31}P and^{13}C) spectroscopy. In case of the IR spectrum of intermediate 3, the presence of IR stretching frequency at 1704 cm^{-1} for aldehydic C=O group, 2739 cm^{-1} for aldehydic proton and the frequency in the range 1156-1190 cm^{-1} for P-O-C(phenyl) confirms the formation of intermediate, **3**. Further in the ^{1}H NMR spectrums of **3** the downfield peak at 10.14 ppm for aldehydic proton also supported the formation of **3**.

In the analysis of tri-Schiff bases **(5a-5f)**, the IR spectrum shows the stretching frequency in between the range of 1630-1650 cm^{-1} indicating the formation of C=N bond validating the complete conversion of the intermediate **3** to desired tri-Schiff bases. In the ^{1}HNMR spectrums of all tri-Schiff bases **(5a-5f)**, the downfield peak value in between 8 to 9 ppm for HC=N proton signifies the structure and the ^{13}C peak value in between 158 to 160 ppm for C=N further validates the formation of tri-Schiff bases **(5a-5f)**.

All the newly synthesized tri-Schiff's bases were evaluated for antibacterial and antifungal activity. In comparison with standard antibacterial penicillin, compounds **5b**, **5e** and **5f** found to be active against *P.Vulgaris* Compounds **5c** and **5f** were found to active against *S.Aureus*. As compared with standard antibacterial compounds, **5b** and **5f** were observed as active against *X.Citri* and compounds **5d**, **5f** were found to be active against *E.cartovora*. In comparison with standard antifungal nystatine, compounds **5d**, **5e** and **5f** were found to be active against *A.alternata* and compounds **5d** and **5f** were found to be active against *C.lunata*. Compound **5f** showed the highest antibacterial activity whereas compound **5e** showed highest antifungal activity.

Biological Activity

All the newly synthesized tri-Schiff's bases **(5a-5f)** were screened for their antibacterial activity against *Proteus vulgaris, Staphylococcus aureus, Xanthomonas citri and Erwinia cartovora*and antifungal activity against *AlternariaAlternata*and *Curvularia lunata* using disc diffusion method[41]. Although no specific trend can be given, still few fruitful highlights are shown in Fig.-1.

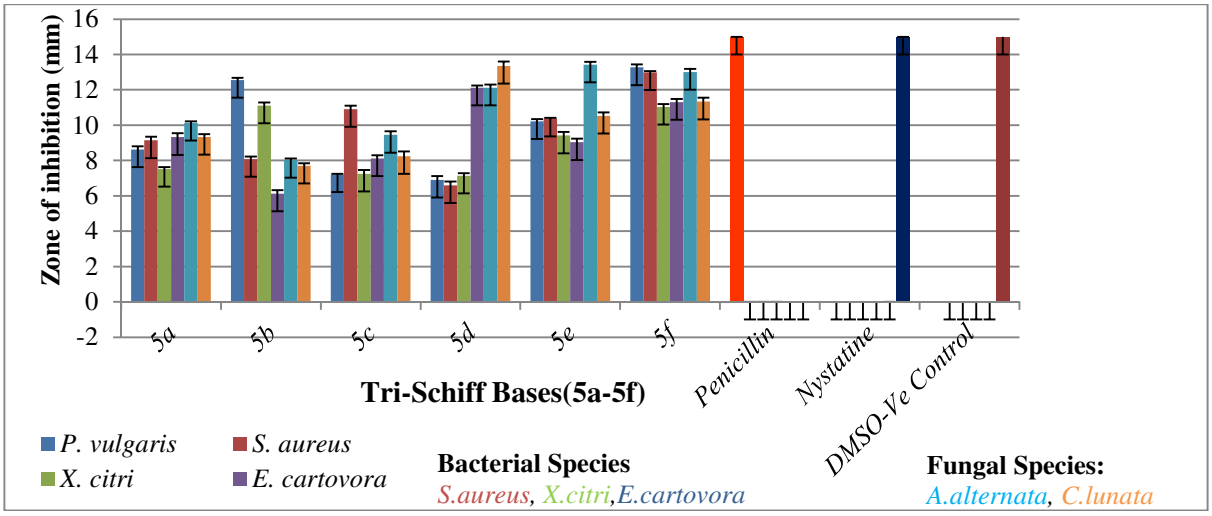


Fig.-1: Antibacterial and Antifungal Activities of Tri-Schiff Bases (5a-5f)

Compound **5f** was found to show strong activity amongst all the synthesized compounds against all the bacterial and fungal pathogens. Compound **5e** was found to show moderate to strong activity against all the bacterial and fungal pathogens studied. In other compounds compound, **5b** was found to show strong activity against bacterial pathogen *P. vulgaris*. Compound **5d** was found to show strong activity against bacterial pathogen *E. cartovora* and both the fungal pathogens *A.Alternata* and *C. lunata*.

CONCLUSION

Wehave developed the efficient method for the synthesis of the intermediate O,O,O-tris(4-formylphenyl) phosphorothioate, **3** using tetrabutylammonium bromide $\{(C_4H_9)_4NBr\}$ as a phase transfer catalyst. The reactive terminal aldehyde groups on the side substituent's of O,O,O-tris(4-formylphenyl) phosphorothioate, **3** readily converted to the promising tri-Schiff's bases **(5a-5f)** by the reaction with the various anilines, **4**. All the tri-Schiff's bases **(5a-5f)** were further screened for their antimicrobial activity and were found to show moderate to good activity.

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