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Microwave assisted synthesis and characterization of novel hydrazone derivatives

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ABSTRACT

A simple and efficient method has been developed for the synthesis of *O*-alkyl alkyl-1-(4-substituted benzylidene) phosphonohydrazone derivatives **(3a-j)** using silica supported microwave irradiation technique under solvent free conditions. The series of phosphonohydrazone derivatives were synthesized by the condensation reaction of *O*-alkyl alkylphosphorohydrazides **(1a-e)** with substituted benzaldehydes. The synthesized compounds were structurally confirmed by elemental analysis, FT-IR, ^{1}H NMR and mass spectroscopy.

KEYWORDS

Hydrazides;
Microwave irradiation;
Phosphonohydrazones;
Silica.

INTRODUCTION

Hydrazones have attracted attention as an important class of the organic chemistry in the field of drugs and pharmaceuticals. These compounds are widely used as anti-inflammatory[1], anticancer[2], analgesic[3], anticonvulsant[4], antituberculous[5], antiproliferative[6], antitumor[7,8], anti-HIV[9], antimycobacterial[10] and antimicrobial activity[11]. Other than their biological importance, hydrazone and their derivatives are used to synthesize various heterocyclic compounds due to the capability to react with electrophilic and nucleophilic reagents. For example, synthesis of indoles[12], 4-thiazolidin-4-ones, azetidines[13] by [2+2] cycloaddition and various five-membered heterocyclic compounds by 1,3-dipolar cycloaddition of azomethine imines that are formed by a 1,2-*H*-shift[14].

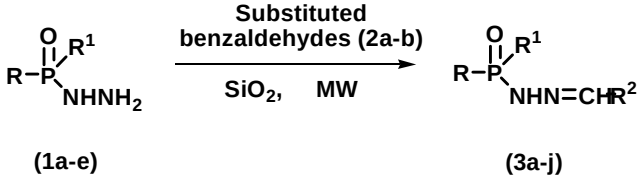
Research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacology activity. Generally, these compounds are synthesized by the condensation reaction of substituted hydrazines/hydrazides with aldehydes and ketones in solvents like ethanol, butanol, glacial acetic acid, ethanol-glacial acetic acid[1]. These are also synthesized by the reaction of hydrazide and carbonyl compounds in presence of polystyrene sulfonic acid in aqueous medium using microwaves[15], only microwaves[16], acidic alumina[17], ultrasound irradiation in aqueous medium[18]. However, the synthesis of phosphorohydrazones has not been fully explored. There have been only few reports for the synthesis of phosphorohydrazones, which have several drawbacks such as use of carcinogenic solvent, long reaction time and formation of several by-products. Herein, a new method for the preparation of phosphonohydrazones is reported. It was found that silica supported microwave irradiation technique capable to producing high yields to phosphonohydrazones by condensation of

phosphonohydrazides with aromatic aldehydes under mild conditions. The method have advantages, such as ease of execution and work-ups, fast rate of reactions, higher yields, solvents-less reaction conditions and low cost. Chromatographic grade silica has many applications as a heterogeneous catalyst either by itself as a support for other reagents[19]. This prompted us to explore the utility of solid support reaction under microwave irradiation for the synthesis of phosphonohydrazones.

Keeping this observation in view and in continuation of our study on the synthesis of biologically active heterocycles[20-22], in this paper presents the synthesis of a series of some new hydrazones.

RESULTS AND DISCUSSION

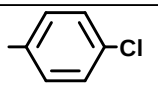
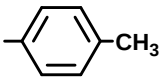
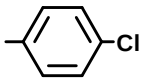
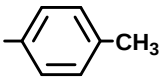
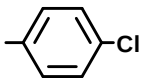
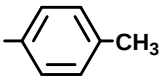
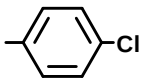
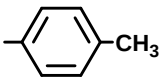
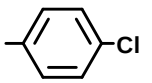
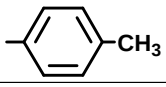
Inspired by the concept of microwave heating, we thought that *O*-alkyl alkyl-1-(4-substituted benzylidene) phosphonohydrazones **(3a-j)** could be prepared from *O*-alkyl alkylphosphorohydrazides **(1a-e)** (Scheme 1). In this regard, initially, we prepared *O*-alkyl alkylphosphorohydrazides **(1a-e)** by reported method[23]. After obtaining the *O*-alkyl alkylphosphorohydrazides **(1a-e)**, we optimized the reaction conditions for synthesis of hydrazones. In this regard, several reactions of *O*-alkyl alkylphosphorohydrazides with substituted benzaldehydes were performed under different conditions. When hydrazides **(1a-e)** were reacted with substituted benzaldehydes under microwave irradiation using silica as solid support, obtained maximum yields. These reactions were monitored by TLC. After optimization, the general applicability of the method was tested by reacting various *O*-alkyl alkylphosphorohydrazides **(1a-e)** with substituted benzaldehydes and these results are summarized in TABLE 1. The compounds **(3a-j)** was characterized by IR, NMR, MS and elemental analysis and results are complied in experimental section.



(1a-e) (3a-j)

Scheme 1 : Synthesis of hydrazone derivatives

TABLE 1 : Physical data of the newly synthesized compounds (3a-j)

Entry	R	R^1	R^2	Reaction time (min)	m. p. (^{0}C)	Yield (%)
3a	$^iC_3H_7$	OC_3H_7		5.0	155	76
3b	$^iC_3H_7$	OC_3H_7		6.0	159	71
3c	$^iC_3H_7$	OC_4H_9		7.0	164	78
3d	$^iC_3H_7$	OC_4H_9		8.0	172	81
3e	$^iC_3H_7$	OC_5H_{11}		8.0	155	83
3f	$^iC_3H_7$	OC_5H_{11}		9.0	158	73
3g	C_6H_5	OC_3H_7		7.0	163	79
3h	C_6H_5	OC_3H_7		7.0	179	65
3i	C_6H_5	OC_5H_{11}		10.0	210	73
3j	C_6H_5	OC_5H_{11}		10.0	209	79

EXPERIMENTAL SECTION

General procedures

All the melting points were determined in open capillary tubes and are uncorrected. The purity of the newly synthesized compounds was checked by TLC on aluminium oxide 60 F_{254} plates (Merck) and spots were visualized by exposing the dry plates in iodine vapor. The IR spectra were recorded on a Nicolet-Magna-FT-IR-550 spectrometer in using KBr pellets. ^{1}H NMR spectra were run on model DRX 300 at 300.13 MHz in $CDCl_3$ and mass spectra on a LCMS instrument. The elemental analysis (C, H, N) of compounds was performed on Carlo Erba -1108 element analyzer. Their results were found to be in good agreement with the calculated values.

Synthesis of phosphonohydrazones (4a-i)

To O-alkyl alkyl phosphonohydrazides (0.01M)

taken in conical flask, SiO_2 (1 gm) and substituted benzaldehydes (0.01M) were added and mixed well. The reaction was microwave irradiation at 180 W for 5-10 minutes. The progress of the reaction was monitored by TLC after drawing a few milligrams of the reaction mixture and extracting with ether. After the disappearance of the phosphonohydrazides spot on the TLC, the reaction mass was washed with ether and solvent was evaporated. Finally desired crude product was triturated with dry ether gave white crystalline powder which was recrystallized by ethanol-ether (7:3).

O-Propyl isopropyl-1-(4-chlorobenzylidene) phosphorohydrazone (3a)

IR (KBr, υ_{max}/cm^{-1}) : 3320 (N-H), 2895 (C-H), 1632 (C=N), 1245 (P=O), 1085 (P-O-C), 815(C-Cl), 705 (P-C). Anal. Calcd.(%) for $C_{13}H_{20}ClN_2O_2P$: C, 51.58; H, 6.66; N, 9.25. Found: C, 51.60; H, 6.60; N, 9.30. ^1H NMR ($CDCl_3$, δ ppm): 0.90(t, J = 6.9 Hz, 3H, CH_3), 1.11(dd, J_{PH} = 20.5 Hz, 6H, CH_3), 1.18(m, J = 7.3 Hz, 2H, CH_2), 1.95 (m, J_{PH} = 16.8 Hz, 1H, CH), 4.03(q, J_{PH} = 18.3 Hz, 2H, CH_2), 4.27(br s, 1H, NH), 7.35-7.60 (m, 4H, Ar-H). LCMS (EI): m/z, 303 ($M+H^+$).

O-Propyl isopropyl-1-(4-methylbenzylidene) phosphorohydrazone (3b)

IR (KBr, υ_{max}/cm^{-1}) : 3305 (N-H), 2910 (C-H), 1630 (C=N), 1240 (P=O), 1083 (P-O-C), 695 (P-C). Anal. Calcd. (%) for $C_{14}H_{23}N_2O_2P$: C, 59.56; H, 8.21; N, 9.92 . Found: C, 59.60; H, 8.25; N, 9.95. ^1H NMR ($CDCl_3$, δ ppm): 0.93(t, J = 6.8 Hz, 3H, CH_3), 0.98(d, J = 7.3 Hz, 3H, CH_3), 1.07 (dd, J_{PH} = 20.6 Hz, 6H, CH_3), 1.15(m, J = 7.2 Hz, 2H, CH_2), 2.05 (m, J_{PH} = 16.5 Hz, 1H, CH), 3.95(q, J_{PH} = 19.4 Hz, 2H, CH_2), 4.25(br s, 1H, NH), 7.35-7.60(m, 4H, Ar-H). LCMS (EI): m/z, 283 ($M+H^+$).

O-Butyl isopropyl -1-(4-chlorobenzylidene) phosphorohydrazone (3c)

IR (KBr, υ_{max}/cm^{-1}) : 3305 (N-H), 2895 (C-H), 1625 (C=N), 1238 (P=O), 1090 (P-O-C), 815(C-Cl), 705 (P-C). Anal. Calcd. (%) for $C_{14}H_{22}ClN_2O_2P$: C, 53.08; H, 7.00; N, 8.84. Found:C, 53.10; H, 7.05; N, 8.82. ^1H NMR ($CDCl_3$, δ ppm): 0.95 (t, J = 7.5 Hz, 3H, CH_3), 1.07(dd, J_{PH} = 22.3 Hz, 6H, CH_3),1.15(m, J = 7.1 Hz, 3H, CH_2), 1.28 (m, J = 7.6 Hz, 3H, CH_2), 2.05 (m, J_{PH} = 18.1 Hz, 1H, CH), 4.05(q, J_{PH} = 18.7 Hz, 2H, CH_2), 4.27 (d, J_{PH} = 17.6 Hz, 1H, NH), 7.35-7.60(m, 4H, Ar-H). LCMS (EI): m/z, 317 ($M+H^+$).

O-Butyl isopropyl-1-(4-methylbenzylidene) phosphorohydrazone (3d)

IR (KBr, υ_{max}/cm^{-1}) : 3300 (N-H), 2890 (C-H), 1630 (C=N), 1245 (P=O), 1090 (P-O-C), 697 (P-C). Anal. Calcd. (%) for $C_{15}H_{25}N_2O_2P$: C, 60.79; H, 8.50; N, 9.45. Found:C, 60.80; H, 8.55; N, 9.50. ^1H NMR ($CDCl_3$, δ ppm): 0.95(t, J = 7.3 Hz, 3H, CH_3), 1.07(dd, J_{PH} = 21.7 Hz, 6H, CH_3), 1.15(m, J = 7.5 Hz, 3H, CH_2), 1.30 (m, J = 7.6 Hz, 3H, CH_2), 1.95 (m, J_{PH} = 16.9 Hz, 1H, CH), 4.02(q, J_{PH} = 20.3 Hz, 2H, CH_2), 4.27 (d, J_{PH} = 18.5 Hz, 1H, NH), 7.35-7.60(m, 4H, Ar-H). LCMS (EI): m/z, 297 ($M+H^+$).

O-Pentyl isopropyl -1-(4-chlorobenzylidene) phosphorohydrazone (3e)

IR (KBr, υ_{max}/cm^{-1}) : 3295(N-H), 2907 (C-H), 1628 (C=N), 1245 (P=O), 1095 (P-O-C), 815(C-Cl), 705(P-C). Anal. Calcd. (%) for $C_{15}H_{24}ClN_2O_2P$: C, 54.46; H, 7.31; N, 8.47. Found: C, 54.50; H, 7.30; N, 8.50. ^1H NMR ($CDCl_3$, δ ppm): 0.95(t, J = 7.9 Hz, 3H, CH_3), 1.07(dd, J_{PH} = 21.4 Hz, 6H, CH_3), 1.18(m, J =7.3 Hz, 3H, CH_2), 1.25(m, J = 8.5 Hz, 3H, CH_2), 1.35(m, J = 8.3 Hz, 3H, CH_2), 2.05 (m, J_{PH} = 17.6 Hz, 1H, CH), 3.95(q, J_{PH} = 19.5 Hz, 2H, CH_2), 4.15 (d, J_{PH} = 18.2 Hz, 1H, NH), 7.35-7.60(m, 4H, Ar-H). LCMS (EI): m/z, 331 ($M+H^+$).

O-Pentyl isopropyl-1-(4-methylbenzylidene) phosphorohydrazone (3f)

IR (KBr, υ_{max}/cm^{-1}) : 3305 (N-H), 2905 (C-H), 1630 (C=N), 1245 (P=O), 1090 (P-O-C), 705(P-C). Anal. Calcd. (%) for $C_{16}H_{27}N_2O_2P$: C, 61.92; H, 8.77; N, 9.03. Found: C, 61.95; H, 8.75; N, 9.05. ^1H NMR ($CDCl_3$, δ ppm): 0.95(t, J = 7.9, 3H, CH_3), 0.95(d, 3H, CH_3), 1.07(dd, J_{PH} = 21.4 Hz, 6H, CH_3), 1.18(m, J = 7.3 Hz, 3H, CH_2), 1.25(m, J = 8.5 Hz, 3H, CH_2), 1.35(m, J = 8.3 Hz, 3H, CH_2), 2.05 (m, J_{PH} = 17.6 Hz, 1H, CH), 3.95(q, J_{PH} = 19.5 Hz, 2H, CH_2), 4.15 (d, J_{PH} =18.2 Hz, 1H, NH), 7.35-7.60(m, 4H, Ar-H). LCMS (EI): m/z, 311 ($M+H^+$).

O-Propyl phenyl-1-(4-chlorobenzylidene) phosphorohydrazone (3g)

IR (KBr, υ_{max}/cm^{-1}) : 3320 (N-H), 2890 (C-H),

1630 (C=N), 1235 (P=O), 1090 (P-O-C), 813(C-Cl), 695 (P-C). Anal. Calcd (%) for $C_{16}H_{18}ClN_2O_2P$: C, 57.07; H, 5.39; N, 8.32. Found: C, 50.10; H, 5.35; N, 8.30. ^1H NMR ($CDCl_3$, δ ppm): 1.15(t, J = 6.5 Hz, 3H, CH_3), 1.35(q, J = 7.4 Hz, 2H, CH_2), 4.15(q, J_{PH} = 19.4 Hz, 2H, CH_2), 4.22 (d, J_{PH} = 18.5 Hz, 1H, NH), 7.25-150 (m, 9H, C_6H_5). LCMS (EI): m/z, 337 ($M+H^+$).

O-Propyl phenyl-1-(4-methylbenzylidene) phosphorohydrazone (3h)

IR (KBr, υ_{max}/cm^{-1}) : 3315 (N-H), 2905 (C-H), 1625 (C=N), 1235 (P=O), 1090 (P-O-C), 695 (P-C). Anal. Calcd. (%) for $C_{17}H_{21}N_2O_2P$: C, 64.55; H, 6.69; N, 8.13. Found: C, 64.50; H, 6.70; N, 8.15. ^1H NMR ($CDCl_3$, δ ppm): 0.93(d, J = 6.5 Hz, 3H, CH_3), 1.15(t, J = 7.5 Hz, 3H, CH_3), 1.35(q, J = 7.4 Hz, 2H, CH_2), 4.15(q, J_{PH} = 17.3 Hz, 2H, CH_2), 4.20 (d, J_{PH} = 20.4 Hz, 1H, NH), 7.25-150 (m, 9H, C_6H_5). LCMS (EI): m/z, 317 ($M+H^+$).

O-Pentyl phenyl-1-(4-chlorobenzylidene) phosphorohydrazone (3i)

IR (KBr, υ_{max}/cm^{-1}): 3305 (N-H), 2905 (C-H), 1630 (C=N), 1240 (P=O), 1085 (P-O-C), 805(C-Cl), 705 (P-C). ^1H NMR ($CDCl_3$, δ ppm): 0.90(t, J = 6.9 Hz, 3H, CH_3), 1.13(m, J = 8.3 Hz, 3H, CH_2), 1.22(m, J = 7.6 Hz, 3H, CH_2), 1.35(m, J = 7.6 Hz, 3H, CH_2), 3.97(q, J_{PH} = 18.7 Hz, 2H, CH_2), 4.55 (d, J_{PH} =17.9 Hz, 1H, NH), 7.25-7.50 (m, 9H, C_6H_5). LCMS (EI): m/z, 365 ($M+H^+$). Anal. Calcd. (%) for $C_{18}H_{22}ClN_2O_2P$: C, 59.26; H, 6.08; N, 7.68. Found: C, 59.30; H, 6.10; N, 7.70.

O-Pentyl phenyl-1-(4-methylbenzylidene) phosphorohydrazone (3j)

IR (KBr, υ_{max}/cm^{-1}) : 3309 (N-H), 2908 (C-H), 1630 (C=N), 1255 (P=O), 1090 (P-O-C), 693 (P-C). Anal. Calcd. (%) for $C_{19}H_{25}N_2O_2P$: C, 66.26; H, 7.32; N, 8.13. Found: C, 66.30; H, 7.35; N, 8.10. ^1H NMR ($CDCl_3$, δ ppm): 0.95 (t, J = 6.9 Hz, 3H, CH_3), 1.03(t, J = 7.8 Hz, 3H, CH_3), 1.15(m, J = 8.3 Hz, 3H, CH_2), 1.23(m, J = 8.1 Hz, 3H, CH_2), 1.37(m, J = 7.4 Hz, 3H, CH_2), 2.92 (Broad s, 2H, NH_2), 3.97(q, J_{PH} = 19.4 Hz, 2H, CH_2), 4.56 (d, J_{PH} =18.9 Hz, 1H, NH), 7.25-7.50 (m, 9H, C_6H_5). LCMS (EI): m/z, 345 ($M+H^+$).

CONCLUSION

In conclusion, we have synthesized various phosphonohydrazones **(3a-j)** with excellent yields. The main advantage of this method is that reactions were found clean and had operational simplicity. The synthesized compounds could be useful for searching newer antimicrobial molecules.

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