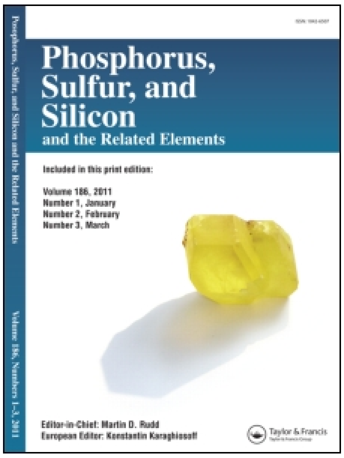

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Silica-Gel-Catalyzed Conversion of Stabilized Phosphorus Ylides to Benzo[*e*][1,3]Thiazocin Derivatives

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SILICA-GEL–CATALYZED CONVERSION OF STABILIZED PHOSPHORUS YLIDES TO BENZO[*e*][1,3]THIAZOCIN DERIVATIVES

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The reaction between triphenylphosphine, dialkylacetylenedicarboxylates, and N-benzoyl thiourea derivatives leads to intermediates such as vinyltriphenylphosphonium salts, which undergo Michael addition to produce the highly functionalized phosphorus ylides containing alkyl groups in excellent yields. Using silica gel as a catalyst, the conversion of the stabilized phosphorus ylides to benzo[e][1,3]thiazocin derivatives in solvent free conditions at 90°C in fairly high yields is achieved.

Keywords Benzo[*e*][1,3]thiazocin derivatives; benzoyl isothiocyanate; *N*-benzoyl thiourea derivatives; dialkylacetylenedicarboxylates; silica gel

INTRODUCTION

Phosphorus ylides are reactive compounds that participate in many reactions of value in the synthesis of organic products.[1–10] The development of the modern chemistry of natural and physiologically active compounds would have been impossible without the phosphorus ylides.[11–16] These compounds have attained great significance as widely used reagents for molecular building blocks by the formation of carbon–carbon double bonds.[17]

There are many studies on the reaction between trivalent phosphorus nucleophiles and α,β-unsaturated carbonyl compounds using phenols, imides, amides, enols, oximes, and alcohols as reaction adjuncts. Unsaturated esters such as dialkyl acetylenedicaboxylates have been employed as Michael substrates in the presence of protic reagents.[18–30] In this article, we report the catalytic role of silica gel powder in the conversion of stabilized phosphorus ylides to benzo[*e*][1,3]thiazocin derivatives in solvent-free thermal conditions in fairly high yields.

RESULTS AND DISCUSSION

Our new synthetic method that leads to the title compounds is given in Scheme 1. The reactions of *N*-benzoyl thiourea derivatives (**3**), which were derived from the addition of

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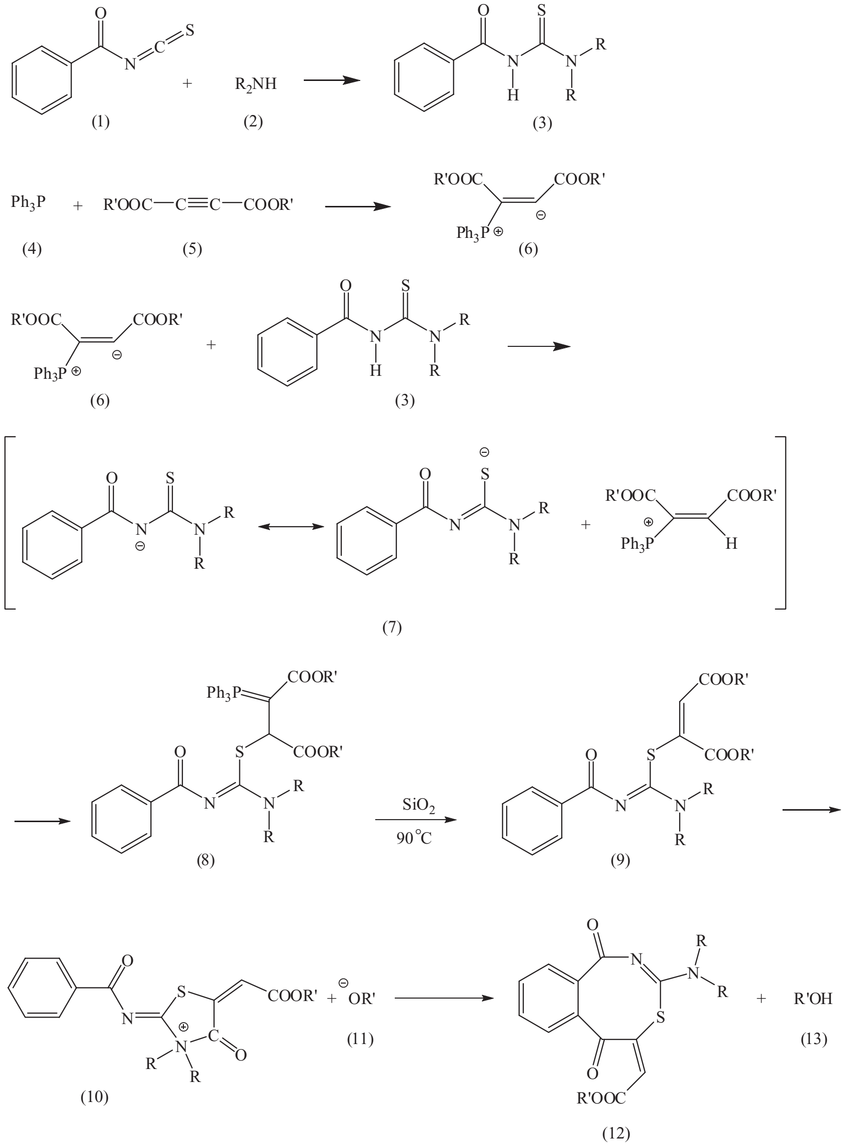
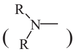


12	$\mathrm{R_2N{-}}$	R'
A	diisopropylamine	CH_3
B	diisopropylamine	CH_3-CH_2
C	piperidine	CH_3
D	piperidine	CH_3-CH_2

Scheme 1

secondary amines (**2**) to benzoyl isothiocyanate (**1**), with acetylenic ester (**5**) in the presence of triphenylphosphine (**4**) proceed in CH_2Cl_2 at –5°C to produce ylide (**8**). The TLC test indicated formation of the ylide in CH_2Cl_2. Silica gel powder was found to catalyze the conversion of ylide (**8**) to benzo[*e*][1,3]thiazocin derivatives (**12**) in solvent-free conditions at 90°C in fairly good yields.

The ylide (**8**) may result from the initial addition of triphenylphosphine (**4**) to the acetylenic ester (**5**) and concomitant protonation of the 1:1 adduct, followed by the electrophilic attack of the vinyltriphenylphosphonium cation to the anion of the benzoyl thiourea derivatives (**7**). The silica gel was found to catalyze the conversion of ylides (**8**) to vinylated compounds (**9**) in solvent-free conditions.

The neighboring group is an amine, containing nitrogen with unshared electrons, and this amine () of compounds **9** helps to push out the alkoxy anion, in order to get the intermediate ammonium ion. This intermediate undergoes nuclophilic attack by the phenyl and yields the product **12**. The TLC indicated that the reaction was completed in the presence of silica gel at 1 h, but this reaction was completed at reflux temperature (CH_2Cl_2 as solvent) after 120 h. In this reaction, we have used $MgSO_4$, MgO, ZnO, $ZnSO_4$, Al_2O_3, $Al_2(SO_4)_3$, $NaHSO_4$, CuO, $Cu(NO_3)_2$ $CuSO_4$, $FeSO_4$, $Mn(NO_3)_2$, and MnO_2 powder instead of silica gel, but no corresponding product **12** was observed.

The structures were deduced from their melting points, IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and mass spectrometry.

CONCLUSION

In summary, we believe the reported method offers a mild, simple, and efficient route for the preparation of benzo[*e*][1,3]thiazocin derivatives. Its ease of workup, high yield, and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

EXPERIMENTAL

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. TLC and NMR indicated that there is no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-300 AVANCE spectrometer at 300.13 and 75.467 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. Flash chromatography columns were prepared from Merck silica gel powder.

General Procedure for the Preparation of Compounds 12a–d

To a solution of benzoyl isothiocyanate **1** (0.163 g, 1 mmol) and secondary amine **2** (1 mmol) in dry CH_2Cl_2 (5 mL) magnetically stirred for 2 h, triphenylphosphine **4** (0.262 g, 1 mmol) and finally a solution of acetylenic ester **5** (1mmol) dropwise in dry CH_2Cl_2 (3 mL) was added at –5 was added C temperature over 10 min. The mixture was allowed to warm to room temperature. Silica gel powder (2 g) was added, and the solvent was evaporated. The dry materials were heated for 1 h at 90°C and then placed over a column of silica gel

(10 g). The column chromatography was washed using ethyl acetate/light petroleum ether (1:10) as an eluent. The solvent was removed under reduced pressure and the products were obtained. The characterization data of the compounds (**12a–d**) are given below.

Selected Data for (E)-Methyl 2-((Z)-3-(Diisopropylamino)-1,6-dioxo-1H-benzo[e][1,3]thiazocin-5(6H)-ylidene)acetate (12a)

White crystals; mp: 81.4–82.9°C; Yield: 82%. IR (KBr)(ν_{max}, cm^{-1}): 3020, 2965, 1706 and 1258. ^{1}H NMR ($CDCl_3$) δ_H: 1.42 (12H, d, $^3J_{HH} = 6.9$ Hz, CH_3 of isopropyl), 3.74 (3H, s, OCH_3), 3.92–3.96 (2H, m, CH of isopropyl), 7.27 (1H, s, CH of vinylic), 7.39–7.42 and 7.81–7.84 (4H, m, arom). ^{13}C NMR ($CDCl_3$) δ_C: 20.02 (4C, CH_3 of isopropyl) 51.15 (1C, OCH_3), 51.44 (2C, CH of isopropyl), 127.38, 128.78 and 129.95 (5C of =CH), 128.86, 130.86 and 135.12 (4C), 160.65, 162.62 and 168.01 (3C of C=O). MS: *m/z* (%); 374 (M^+, 5), 318 (60), 275(100), 261(94), 229(19), 89(18), 43(32). Anal. Calcd. For $C_{19}H_{22}N_2O_4S$ (374.45): C 60.94, H 5.92, N 7.48. Found: C 60.81, H 5.79, N 7.41%.

Selected Data for (E)-Ethyl 2-((Z)-3-(Diisopropylamino)-1,6-dioxo-1H-benzo[e][1,3]thiazocin-5(6H)-ylidene)acetate (12b)

Yellow crystals; mp: 94.0–95.1°C; Yield: 79%. IR (KBr)(ν_{max}, cm^{-1}): 3031, 2966, 1700 and 1260. ^{1}H NMR ($CDCl_3$) δ_H: 1.26 (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3 of Et); 1.42 (12, d, $^3J_{HH} = 7.0$ Hz, CH_3 of isopropyl); 3.91–3.95 (2H, m, CH of isopropyl); 4.21 (2H, q, $^3J_{HH} = 7.1$, CH_2 of Et), 7.27 (1H, s, CH of vinylic); 7.38–7.41 and 7.80–7.84 (4H, m, arom). ^{13}C NMR ($CDCl_3$) δ_C: 14.34 (1C, CH_3 of Et); 20.04 (4C, CH_3 of isopropyl); 51.14 (1C, CH_2 of Et); 60.31 (2C, ch of isopropyl); 127.32, 128.68 and 129.99 (5C of =CH); 128.79, 130.90 and 135.28 (4C), 159.76, 162.25 and 167.98 (3C of C=O). MS: *m/z* (%); 388 (M^+, 3), 332 (56), 289 (100), 244 (81), 160 (15), 101 (21), 77(25), 58 (31), 45 (28). Anal. Calcd. For $C_{20}H_{24}N_2O_4S$ (388.48): C 61.83, H 6.23, N 7.21. Found: C 61.75, H 6.15, N 7.19%.

Selected Data for (E)-Methyl 2-((Z)-1,6-Dioxo-3-(piperidin-1-yl)-1H-benzo[e][1,3]thiazocin-5(6H)-ylidene)acetate (12c)

White crystals; mp: 99.5–100.6°C; Yield: 75%. IR (KBr)(ν_{max}, cm^{-1}): 3015, 2997, 2962, 1715 and 1245. ^{1}H NMR ($CDCl_3$) δ_H: 1.68–1.72 (6H, m, CH_2 of piperidine); 3.57–3.59 (4H, m, CH_2 of piperidine); 3.74 (3H, s, OCH_3); 7.27 (1H, s, CH of vinylic); 7.39–7.41 and 7.75 (4H, m, arom). ^{13}C NMR ($CDCl_3$) δ_C: 22.97, 23.76 and 49.17 (5C, CH_2); 51.53 (1C, OCH_3); 127.54, 128.90 and 129.76 (5C of =CH); 128.79, 130.86 and 134.90 (4C); 160.38, 162.44 and 170.90 (3C of C=O). MS: *m/z* (%); 358 (M^+, 3), 300 (100), 275(77), 167(18), 149 (40), 85 (21), 71 (19), 58 (47), 43 (95). Anal. Calcd. For $C_{18}H_{18}N_2O_4S$ (358.41): C 60.32, H 5.06, N 7.82. Found: C 60.27, H 4.98, N 7.75%.

Selected Data for (E)-Ethyl 2-((Z)-1,6-Dioxo-3-(piperidin-1-yl)-1H-benzo[e][1,3]thiazocin-5(6H)-ylidene)acetate (12d)

Viscous oil; Yield: 71%. IR (KBr)(ν_{max}, cm^{-1}): 3027, 2936, 1708 and 1243. ^{1}H NMR ($CDCl_3$) δ_H: 1.24 (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3 of Et); 1.68–1.70 (6H, m, CH_2 piperidine); 3.57–3.58 (4H,m, CH_2 of piperidine); 4.20 (2H, q, $^3J_{HH} = 7.1$ Hz, CH_2 of Et); 7.27 (1H, s, CH vinylic), 7.37–7.39 and 7.73–7.76 (4H, m, arom). ^{13}C NMR ($CDCl_3$) δ_C: 14.25 (1C, CH_3); 23.76, 23.99 and 49.17 (5C, CH_2); 60.46 (1C, OCH_2), 127.49, 128.82 and 129.79

(5C, =CH); 127.83, 130.86 and 135.01 (4C); 159.99, 162.05 and 170.84 (3C of C=O). MS: *m/z* (%); 372 (M^+, 4), 314 (100), 289 (71), 269 (20), 242 (10), 217 (8), 133 (38), 85 (18), 45 (21). Anal. Calcd. For $C_{19}H_{20}N_2O_4S$ (372.44): C 61.27, H 5.41, N 7.52. Found: C 61.24, H 5.37, N 7.48%.

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