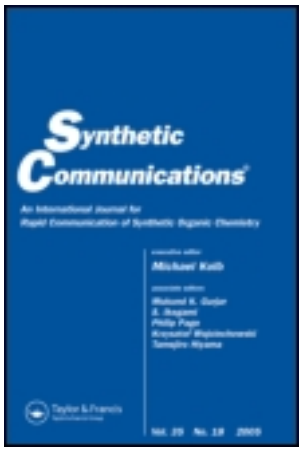

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Solvent-Free Synthesis of 1,5-Benzothiazepines and Benzodiazepines on Inorganic Supports

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ABSTRACT

1,5-Benzothiazepines and 1,5-benzodiazepines have been synthesized in solvent-free conditions from chalcones and *o*-aminothiophenol or *o*-phenylenediamine in the presence of inorganic support. Silica gel was found to be an effective support for the synthesis of 1,5-benzothiazepines, whereas alumina was effective for the synthesis of 1,5-benzodiazepines.

Key Words: Benzothiazepine; Benzodiazepine; Silica gel; Alumina; Solvent-free synthesis.

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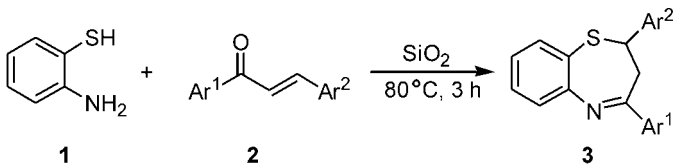
Benzothiazepines and benzodiazepines are very important compounds because of their pharmacological properties, and have become increasingly interesting since 1,5-benzothiazepines show antifungal, antibacterial,[1] antifeedant,[2] analgesic,[3] and anticonvulsant activity.[4] Benzodiazepines are used as tranquilizing, anti-inflammatory and anticonvulsant agents. In addition, 1,5-benzothiazepines and benzodiazepines are used as starting materials for the preparation of fused ring compounds such as triazolo-[5] and oxadiazolo-benzodiazepines.[6] Despite their importance from a pharmacological and synthetic point of view, few methods for the preparation of 1,5-benzodiazepines are reported in the literature. These include condensation reactions of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds,[7] β-haloketones,[8] or ketones in the presence of polyphosphoric acid,[9] silica gel,[9] $Yb(Otf)_3$,[10] MgO and $POCl_3$,[11] Amberlyst-15,[12] and acetic acid under MW.[13] 1,5-Benzodiazepines are also prepared by reaction of α,β-unsaturated ketones with *o*-nitroanilines induced by $TiCl_4$-Sm[14] and *o*-nitrophenylazide induced by SmI_2.[15] 1,5-Benzothiazepines have generally been synthesized by the reaction of *o*-aminothiophenol with α,β-unsaturated ketones.[16] 1,5-benzothiazepines have also been synthesized from *o*-aminothiophenol, ω-bromoacetophenones and aromatic aldehydes,[17] and by the reaction of α,β-unsaturated ketones with bis(2-nitrophenyl)disulfide by use of $TiCl_4/Sm$[18] has been reported. There are few reports on the use of inorganic solid supports such as alumina, silica gel and clay for the synthesis of 1,5-benzodiazepines and benzothiazepines under solvent-free condition. Recently, Danidia reported a solvent-free synthesis of 1,5-benzothiazepines in the presence of a solid support under microwave irradiation.[19]

We report herein the solvent-free synthesis of 1,5-benzodiazepines and benzothiazepines by the reaction of chalcones with *o*-phenylenediamine or *o*-aminothiophenol in the presence of an inorganic solid support. Chalcone reacts with *o*-aminothiophenol in refluxing toluene to afford the adduct, β-phenyl-β-(2-aminophenylmercapto)propiophenone, which could be converted to 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine by cyclization in the presence of an acid catalyst.[16] In contrast, the reaction of chalcone with *o*-aminothiophenol in the presence of silica gel was carried out at 80°C under solvent-free conditions to obtain 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine in one-step.



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The results of the reaction of *o*-aminothiophenol with chalcone in the presence of various solid supports were shown in Table 1. From these results it is obvious that silica gel is the most adaptable solid support for the synthesis of 1,5-benzothiazepines since comparatively higher yield is achieved under same conditions. Acidic alumina was ineffective in spite of being an acidic solid like silica gel.

The reaction of *o*-aminothiophenol with chalcones was carried out without solvent in the presence of silica gel at 80°C for 3 hr to afford the corresponding 1,5-benzothiazepines in good yields (Table 2). In the reaction of *o*-aminothiophenol with chalcones in refluxing toluene, from chalcones with electron-donating substituents such as methyl and methoxy group, only *β*-phenyl-*β*-(2-aminophenylmercapto)-propiophenones were formed, whereas from chalcones with electron-withdrawing substituents such as nitro group, only 1,5-benzothiazepines were formed.[16] In contrast, the reaction using silica gel under solvent-free conditions gave only 1,5-benzothiazepines in good yield independent of the chalcone substituents, with the exception of nitro and hydroxy groups. In the case of chalcones having nitro and hydroxy groups, the yields were lower than that of chalcones with the other substituents. It seems that low reactivity of chalcones having nitro and hydroxy groups is due to these groups being absorbed more strongly on the surface of silica gel than that of a carbonyl group in the same molecule. Therefore the carbonyl group in chalcones having nitro or hydroxy groups is less activated than that in chalcones with the other substituents.

It has been reported previously that the reaction of 2-aminoethanethiol with chalcone in benzene gives a mixture of mono-adducts **4** and **5** or a bis-adduct, depending on the molar ratios used.[20] When the reaction was

Table 1. Reaction of *o*-aminothiophenol **1** with chalcone **2** in the presence of various supports.[a]

Support	Yield of benzothiazepine (%)
Silica gel	87
Acidic alumina	28
Basic alumina	2
Neutral alumina	21
Molecular sieves (5 Å)	30
Kieselguhr	5
None	22

[a]Mole ratio of $\mathbf{1}/\mathbf{2} = 1.5$, support: 2 g, 80°C, 3 hr.

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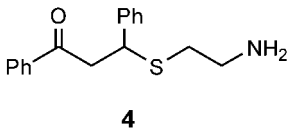
Table 2. Synthesis of 1,5-benzothiazepines.[a]

Compound	Ar^1	Ar^2	Yield[b] (%)
3a	C_6H_5	C_6H_5	87
3b	4-ClC_6H_4	C_6H_5	75
3c	4-$CH_3C_6H_4$	C_6H_5	73
3d	4-$CH_3OC_6H_4$	C_6H_5	61
3e	4-$CH_3OC_6H_4$	C_6H_5	44
3f	C_6H_5	4-ClC_6H_4	78
3g	C_6H_5	4-$CH_3OC_6H_4$	83
3h	C_6H_5	4-$CH_3OC_6H_4$	74
3i	C_6H_5	4-HOC_6H_4	44
3j	C_6H_5	4-$NO_2C_6H_4$	68

[a]Mole ratio **1**/**2** = 1.5, 80°C, 3 hr, SiO_2 (2 g).
[b]Isolated yield.

carried out in the presence of silica-gel under solvent-free condition, the tetrahydrothiazepine **6** was obtained and no other adducts were formed.



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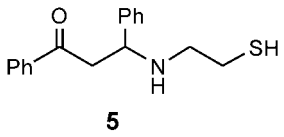

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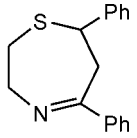

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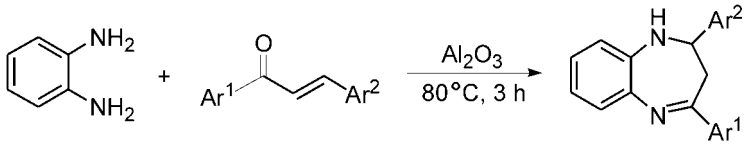
The reaction of chalcones with o-phenylenediamine was performed in the presence of alumina (neutral) under solvent-free conditions at 80°C for 3 hr to afford the corresponding 2,4-dihydro-1*H*-1,5-benzodiazepines in good yield. The results are summarized in Table 3.



7 **2** **8**

Alumina was most effective among the solid supports tested. Silica gel was ineffective at promoting the reaction with *o*-phenylenediamine. As shown in Table 3, both chalcones with electron-donating groups and with electron-withdrawing groups except for nitro and hydroxy groups reacted with *o*-phenylenediamine without any significant difference to give the corresponding 1,5-benzodiazepines in good yields.

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Table 3. Synthesis of 1,5-benzodiazepines.[a]

Compound	Ar^1	Ar^2	Yield[b] (%)
8a	C_6H_5	C_6H_5	81
8b	4-ClC_6H_4	C_6H_5	84
8c	4-$CH_3C_6H_4$	C_6H_5	77
8d	4-$CH_3OC_6H_4$	C_6H_5	70
8e	4-$CH_3OC_6H_4$	C_6H_5	12
8f	C_6H_5	4-ClC_6H_4	89
8g	C_6H_5	4-$CH_3OC_6H_4$	73
8h	C_6H_5	4-$CH_3OC_6H_4$	69
8i	C_6H_5	4-$NO_2C_6H_4$	43

[a]Mole ratio **1**/**2** = 1.5, 80°C, 3 hr, Al_2O_3 (2 g).
[b]Isolated yield.

EXPERIMENTAL

Silica gel and alumina for column chromatography were used as a solid support without any treatment. All reactions were conducted under nitrogen atmosphere. Melting points were uncorrected. IR spectra were recorded on a Horiba FT-710 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H-NMR spectra were recorded on JEOL JNM-LA300 and TMS was used as internal standard. Mass spectra were recorded on JEOL JMS-600H at 70 eV. Products were characterized by comparison of their spectroscopic data (^{1}H-NMR, IR, and Mass) and mps with those reported in the literature.

General Procedure for the Synthesis of 1,5-Benzothiazepines

2,3-Dihydro-2,4-diphenyl-1,5-benzothiazepine (3a). A solution of chalcone (2 mmol) in diethyl ether (30 mL) was mixed with silica gel (4 g) in a 50 mL flask. The solvent was removed by evaporation under reduced pressure. *o*-Aminothiophenol (3 mmol) was added to the mixture, and stirred at 80°C for 3 hr under nitrogen atmosphere. Silica gel was separated by filtration after stirring with ethyl acetate (40 mL) for 15 min at room temperature. After evaporating the solvent under reduced pressure, the crude product was crystallized from methanol to give **3a** (87%) as yellow crystals, m.p. 113–115°C (lit.[21] 114–115°C). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.06 (t, 1H, J = 12.7 Hz), 3.30 (dd, 1H, J = 13.0 Hz, J = 4.8 Hz), 4.98 (dd, 1H, J = 12.6 Hz, J = 4.8 Hz), 7.14 (td, 1H, J = 7.4 Hz, J = 1.5 Hz), 7.23–7.32 (m, 6H), 7.44–7.52 (m, 4H), 7.62 (dd, 1H, J = 7.7 Hz, J = 1.3 Hz), 8.06 (dd, 2H, J = 7.7 Hz, J = 2.0 Hz).

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2,3,6,7-Tetrahydro-5,7-diphenyl-1,4-thiazepine (6). Chalcone (1 mmol) and 2-aminoethanthiol (2 mmol) were dissolved in diethyl ether (20 mL). Silica gel (2 g) was then added to the mixture and stirred for a while followed by removal of the solvent under reduced pressure. The mixture was stirred at 80°C for 3 hr under nitrogen atmosphere. Silica-gel was separated by filtration after eluting the product with ethyl acetate (20 mL). After evaporating the solvent under reduced pressure, the residue was purified by recrystallization from hexane–diethyl ether (1 : 1) to give **6** (55%) as white crystals, m.p. 88–90°C. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ 2.72 (dd, 1H $J = 14.7$ Hz, $J = 6.7$ Hz), 3.02 (dd, 1H, $J = 14.7$ Hz, $J = 9.9$ Hz), 3.59 (d, 1H, $J = 14.1$ Hz), 3.82 (dd, 1H, $J = 14.1$ Hz, $J = 10.2$ Hz), 4.00 (d, 1H, $J = 10.3$ Hz), 4.19 (dd, 1H, $J = 12.5$ Hz, $J = 10.0$ Hz), 4.55 (dd, 1H, $J = 12.6$ Hz, $J = 6.8$ Hz), 7.25–7.70 (m, 10H).

General Procedure for the Synthesis of 1,5-Benzodiazepines

2,3-Dihydro-2,4-diphenyl-1H-1,5-benzodiazpine (8a). Chalcone (1 mmol) and *o*-phenylenediamine (1.5 mmol) were dissolved in diethyl ether (20 mL). Alumina (neutral, 2 g) was then added to the mixture and stirred for a while followed by removal of the solvent under reduced pressure. The mixture was stirred at 80°C for 3 hr under nitrogen atmosphere. Alumina was separated by filtration after eluting the product with ethyl acetate (20 mL). After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica-gel (hexane–ethyl acetate = 10 : 1) to yield **8a** (81%) as a yellow solid, m.p. 129–130°C (lit.[22] 129–129.5°C). ^{1}H-NMR ($CDCl_3$, 300 MHz), δ 3.04 (dd, 1H, $J = 13.5$ Hz, $J = 9.2$ Hz), 3.24 (dd, 1H, $J = 13.5$ Hz, $J = 3.8$ Hz), 3.77 (br s, 1H), 5.19 (dd, 1H, $J = 9.1$ Hz, $J = 3.8$ Hz), 6.82 (dd, 1H, $J = 7.2$ Hz, $J = 1.7$ Hz), 7.00–7.43 (m, 11H), 7.84 (dd, 2H, $J = 7.9$ Hz, $J = 1.7$ Hz).

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