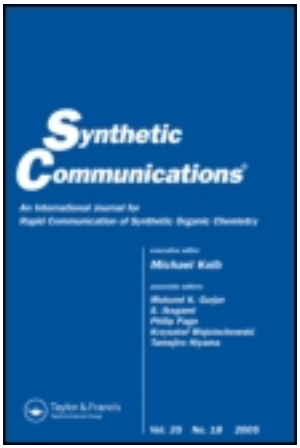

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 29 Sep 2008.

To cite this article: Manickam Bakthadoss & Gandhi Murugan (2008) Simple and New Protocol for the Synthesis of Novel (z)-3-Arylidenebenzothiazepin-4-ones Using Baylis-Hillman Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:20, 3406-3413, DOI: 10.1080/00397910802138249

To link to this article: http://dx.doi.org/10.1080/00397910802138249

Synthetic Communications®, 38: 3406–3413, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802138249

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Simple and New Protocol for the Synthesis of Novel (*z*)-3-Arylidenebenzothiazepin-4-ones Using Baylis–Hillman Derivatives

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Abstract: A simple synthesis of novel (*Z*)-3-arylidene-2,3-dihydrobenzo[*b*][1,4] thiazepin-4(5*H*)-ones from bromo compounds derived from Baylis–Hillman adducts involving selective *S*-alkylation followed by a lactum formation has been described.

Keywords: 2-Amino thiophenol, Baylis–Hillman reaction, benzothiazepinones, diltiazem, thiazesim, *p*-toluenesulfonic acid

INTRODUCTION

During the past few years, the Baylis–Hillman reaction has become increasingly important because it provides multifunctionalized molecules whose applications in synthetic organic chemistry have been well documented in the literature.[1–3] The Baylis–Hillman adducts are also utilized very well as building blocks for many natural products and biologically active molecules.[1–9] Because of multifunctionality present in the suitable positions, the Baylis–Hillman adducts and bromo derivatives were frequently utilized for the synthesis of various types of heterocyclic compounds. Using these compounds, syntheses of a variety of five-, six-, and seven- membered heterocyclic compounds have been reported in the literature, which clearly proves that these Baylis–Hillman adducts

Received February 22, 2008.
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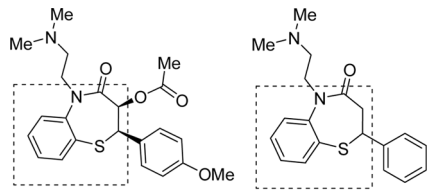
and derivatives are novel sources for the synthesis of a wide range of heterocyclic compounds.[1–3]

Thiazepinones are pharmalogically important compounds for the treatment of cancer and heart and inflammatory diseases. These heterocycles help treat disease by acting as inhibitors to angitensin converting enzyme (ACE), neutral endopeptidase (NEP),[10] and leukocyte adherence.[11] Benzothiazepinone moiety is an integral part of diltiazem (1), a representative calcium antagonist used throughout the world as a remedy for angina and hypertension.[12–15] Thiazesim (2) is another important benzothiazepinone skeleton containing a molecule possessing antiplatelet activity.[16] Benzothiazepinone derivatives are also known to possess antidepressant activity.[17]

Because the variety of benzothiazepinone derivatives possess various biological activities, we planned to develop a new synthetic methodology for benzothiazepinone derivatives containing the core unit of diltiazem (1) and thiazesim (2) using Baylis–Hillman chemistry.

In continuation of our interest in the field of Baylis–Hillman chemistry,[18–20] we herein report the first synthetic route for seven-membered (*Z*)-3-arylidene-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-ones from methyl (2*Z*)-2-(bromomethyl)-3-arylprop-2-enoates derived from corresponding Baylis–Hillman adducts.[18]



Diltiazem **(1)** Thiazesim **(2)**

RESULTS AND DISCUSSION

To the best of our knowledge, there is no report available in the literature for the synthesis of seven-membered (*Z*)-3-arylidene-2,3-dihydrobenzo-[*b*][1,4]thiazepin 4(5*H*)-ones until now. We envisaged that the important core benzothiazepin-4-one moiety could be constructed using the (*Z*)-methyl-2-(bromomethyl)arylacrylates (3) derived from Baylis–Hillman adducts. The formation of seven-membered benzothiazepinone can be achieved by selectively tethering the sulfur atom of the *ortho* amino thiophenol with allylic carbon, which is attached to bromine atom of compound (3), at one end and at other end by tethering the nitrogen

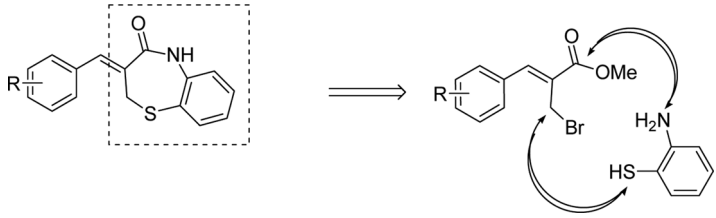


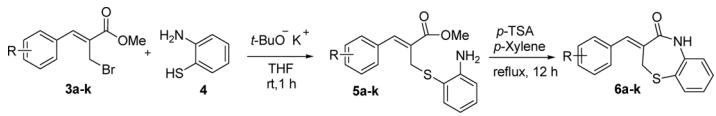
Figure 1. Retro synthetic strategy for the synthesis of benzothiazepinone derivatives.

atom of the *ortho* amino thiophenol with the carbonyl carbon present in the bromo derivative of the Baylis–Hillman adducts (3), shown in Figure 1.

To execute our idea, we first selected the methyl (2*Z*)-2-(bromomethyl)-3-phenylprop-2-enoate **(3a)** prepared from the corresponding Baylis–Hillman adduct and treated with 2-aminothiophenol **(4)** in the presence of potassium-*t*-butoxide in tetrahydrofuran (THF) at room temperature, which successfully led to a selective *S*-alkylated product, (*Z*)-methyl2-((2-aminophe-nylthio)methyl)-3-phenylacrylate **(5a)**, a precursor for the synthesis of (*Z*)-3-benzylidene-2,3-dihydrobenzo[*b*][1,4] thiazepin-4(5*H*)-one **(6a)**. The crude compound **(5a)** was treated with *p*-toluenesulfonic acid using *p*-xylene as a solvent under reflux condition for 12 h and successfully provided the desired (Z)-3-benzylidene-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one **(6a)** in 71% yield, according to Scheme 1. The structure of the compound **(6a)** was confirmed by IR, ^{1}H and ^{13}C NMR, mass spectral data, and elemental analysis.

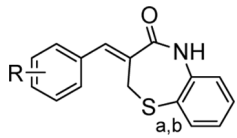
The ^{1}H NMR spectrum of the compound **(6a)** showed a doublet for *S*-attached CH_2 protons at δ 4.00, and NH proton appeared as broad singlet at δ 7.91. The benzylic olefinic proton appeared as a doublet of doublet (due to allylic coupling) at δ 7.49 and the aromatic protons appeared as multiplets in the region of δ 7.04–7.40.

Encouraged by this result, we prepared a variety of (2*Z*)-2-(bromome thyl)-3-arylprop-2-enoates **(3b–k)** from the corresponding Baylis–Hillman



Scheme 1. R=H. 2-Me, 4-Me, 4-Et, 4-Pr, 2-Cl, 3-Cl, 4-Cl, 2,4-dichioro, 4-F, 4-NO_2.

Table 1. Synthesis of (*Z*)-3-arylidene-2,3-dihydrobenzo[*b*][1,4]thiazepin-4-(5*H*)-ones **(6a–k)**



Allybromide	R	Product[a]	Yield[b]	Mp (°C)
3a	H	**6a**	71	168–170
3b	2-Me	**6b**	67	136–138
3c	4-Me	**6c**	70	160–162
3d	4-Et	**6d**	68	118–120
3e	4-^{i}Pr	**6e**	66	122–124
3f	2-Cl	**6f**	67	165–167
3g	3-Cl	**6g**	65	108–110
3h	4-Cl	**6h**	71	112–114
3i	2,4-Dichloro	**6i**	67	194–196
3j	4-F	**6j**	65	185–187
3k	4-No_2	**6k**	67	166–165

[a]All the products gave satisfactory IR, ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), and mass spectral data and elemental analyses.
[b]Yields of the pure product **(6a–k)** obtained after column chromatography.

adducts and treated them with 2-aminothiophenol, which led to the precursors **5b–k**. The crude intermediate products **(5b–k)** were treated with *p*-toluenesulfonic acid under reflux condition for 12 h, which successfully provided the desired (*Z*)-3-arylidene-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-ones **(6b–k)** in 65–71% yield according to Scheme 1. The results are summarized in Table 1.

CONCLUSION

In conclusion, we have successfully developed for the first time a short and simple protocol for facile transformation of Baylis–Hillman bromides into an interesting novel class of seven-membered heterocyclic frameworks containing an important benzothiazepinone moiety, a core unit of diltiazem and thiazesim, thus demonstrating the synthetic potential of the Baylis–Hillman adducts in organic chemistry.

EXPERIMENTAL

General Methods

All melting points are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8000 instrument. NMR spectra were recorded in $CDCl_3$ by using TMS as an internal standard on a Bruker 300 instrument. Mass spectra were recorded on a Jeol DX-303 instrument. Column chromatography was performed on silica gel (100–200 mesh). All reactions were monitored by thin-layer chromatography (TLC) using glass plates coated with Acme silica gel (GF-254).

Typical Experimental Procedure for the Synthesis of Compounds 6a–k

A mixture of trisubstituted allyl bromide **(3a–k)** (2 mmol) and *o*-aminothiophenol (2 mmol) in the presence of potassium *tert*-butoxide (2.4 mmol) in dry THF (10 mL) was stirred at room temperature for 1 h. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated, and the resulting crude mass was diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL). The organic layer was washed with brine (2×20 mL) and dried over anhydrous sodium sulphate. The organic layer was concentrated, which provided a crude mass **(5a–k)**. [The ^{1}H NMR of crude mass **(5a–k)** showed the presence of the NH_2 proton.] The crude product **(5a–k)** was treated with a catalytic amount of *p*-toluene sulphonic acid (0.4 mmol), in *p*-xylene (10 mL), under reflux conditions for 12 h. After the completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure and worked up as mentioned previously, which successfully provided the crude final product **(6a-k)**. The crude final product was purified by column chromatography on silica gel to afford the pure desired product **(6a-k)** in good yield as mentioned in Table 1.

Spectral Data for Selected Compounds

(*Z*)-3-Benzylidene-2,3-dihydrobenzo[b][1,4]thiazepin-4(5*H*)one (**6a**)

Yield: 71%; mp 168–170 °C (white solid). IR (KBr, cm^{-1}); 3171, 1653, 1610. ^{1}H NMR ($CDCl_3$): $\delta = 4.00$ (d, $J = 1.2$ Hz, 2H); 7.04–7.40 (m, 9H); 7.49 (dd, 1H, $J = 1.2$, 7.9 Hz); 7.91 (br s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 35.03$; 122.34; 124.81; 127.73; 128.36; 128.50; 129.11; 129.30; 132.90; 133.29; 134.90; 136.04; 140.27; 170.69. MS (m/z) 268 ($M^+ + 1$). Anal. calcd. for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.12; H, 4.68; N, 5.79.

(*Z*)-3-(2-Methylbenzylidene)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**6b**)

Yield: 67%; mp 136–138 °C (white solid). IR (KBr, cm^{-1}); 3126, 1653, 1610. ^1H NMR ($CDCl_3$): $\delta = 2.06$ (s, 3H); 3.85 (d, $J = 1.2$ Hz, 2H); 6.98–7.35 (m, 8H); 7.46–7.49 (dd, $J = 1.2$, 7.8 Hz, 1H); 7.79 (br s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 19.55$; 35.56; 122.56; 124.93; 125.65; 127.62; 128.33; 128.79; 129.25; 130.12; 133.32; 133.72; 134.02; 134.74; 137.00; 140.89; 171.30. MS m/z 282 ($M^+ + 1$). Anal. calcd. for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.40, H, 5.23, N, 5.02.

(*Z*)-3-(4-Methylbenzylidene)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**6c**)

Yield: 70%; mp 160–162 °C (white solid). IR (KBr, cm^{-1}); 3151, 1658, 1615. ^1H NMR ($CDCl_3$): $\delta = 2.35$ (s, 3H); 4.01 (d, $J = 1.2$ Hz, 2H); 7.01–7.39 (m. 8H); 7.45–7.49 (dd, $J = 1.2$, 7.8 Hz, 1H); 8.91 (br s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 21.29$; 35.00; 122.32; 124.67; 127.78; 129.04; 129.22; 129.40; 132.03; 132.17; 133.17; 136.29; 138.52; 140.29; 170.80. MS m/z 282 ($M^+ + 1$). Anal. calcd. for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.51, H, 5.30, N, 5.11.

(*Z*)-3-(4-Ethylbenzylidene)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**6d**)

Yield: 68%; mp 118–120 °C (white solid). IR (KBr, cm^{-1}); 3205, 1660, 1620. ^1H NMR ($CDCl_3$): $\delta = 1.24$ (t, $J = 7.5$ Hz, 3H); 2.65 (q, $J = 7.5$ Hz, 2H); 4.00 (d, $J = 1.2$ Hz, 2H), 7.03–7.41 (m, 8H); 7.48 (d, $J = 7.5$ Hz, 1H), 7.79 (br s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 15.34$; 28.65; 34.90; 122.18; 124.71; 127.84; 128.03; 129.00; 129.49; 132.01; 132.24; 133.21; 136.44; 140.14; 144.85; 170.50. MS m/z 296 ($M^+ + 1$). Anal. calcd. for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.05; H, 5.45; N, 4.81.

ACKNOWLEDGMENTS

We thank Department of Science & Technology (New Delhi) for the financial support under the fast track scheme. We thank Department of Science & Technology-Fund for Improvement of Science & Technology Infrastructure in Higher Educational Institutions for the funding program at the Department of Organic Chemistry, University of Madras, Chennai.

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