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PII: S0040-4039(14)00220-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.01.153
Reference: TETL 44186

To appear in: *Tetrahedron Letters*

Received Date: 29 October 2013
Revised Date: 29 January 2014
Accepted Date: 31 January 2014

Please cite this article as: Kaishap, P.P., Shekarrao, K., Saikia, P., Gogoi, S., Boruah, R.C., A facile synthesis of benzo[b][1,4]thiazepine derivatives by palladium acetate catalyzed reaction, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.01.153

A facile synthesis of benzo[b][1,4]thiazepine derivatives by palladium acetate catalyzed reaction

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Abstract

The preparation of steroid/nonsteroid fused benzo[b][1,4]thiazepines and 2-arylsubstituted benzo[b][1,4]thiazepines is described from $Pd(OAc)_2$ catalyzed reaction of steroidal/nonsteroidal *β*-halovinyl aldehydes and 2-aminothiophenols in DMF under heating condition.

Keywords: Benzo[b][1,4]thiazepine, steroid, palladium acetate, *β*-bromovinyl aldehyde, 2-aminothiophenol.

The benzo[b][1,4]thiazepine moiety is a well known pharmacophore in medicinal chemistry. Compounds bearing this moiety show different biological activities such as antiHIV, anticancer, anticonvulsant, antianginal, antimicrobial, antifungal etc. They also act as angiotensin converting enzyme inhibitors, calmodulin antagonists, bradykinin receptor agonists and Ca^{2+} antagonist.[1] Some of the widely used benzo[b][1,4]thiazepine drugs are shown in Figure 1. The first benzo[b][1,4]thiazepine derivative diltiazem (Figure 1) is used widely as an antihypertensive drug due to its potent calcium channel blocking property. Similarly, benzo[b][1,4]thiazepine derivative clentiazem is used clinically for its cardiovascular action, quetiapine is used as an atypical antipsychotic agent and thiazesim is used as an antidepressant (Figure 1).

It is known that fusion of a heterocyclic ring with the skeleton of a steroidal molecule alters the activity of the molecule. Because of the remarkable biological activities of these steroids

fused with heterocycles, enormous efforts have been made by different research groups to synthesize a wide variety of these heterosteroids.[2]

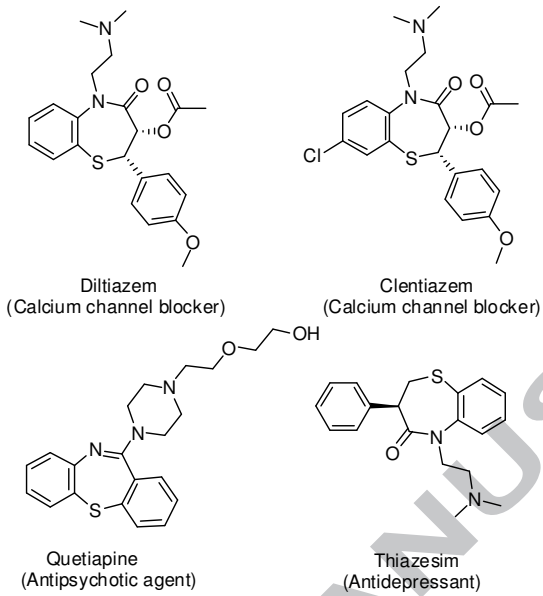
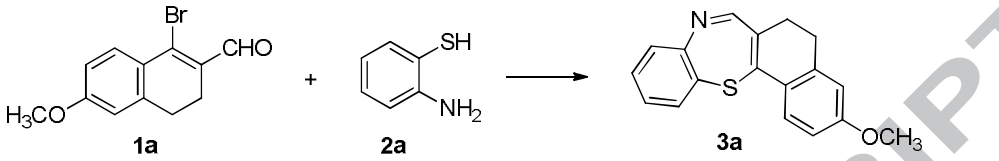


Figure 1: Examples of some clinically used 1,5-benzothiazepine derivatives

There are various synthetic methods reported in the literature for the synthesis of 2,4-disubstituted benzo[b][1,4]thiazepine. For example, recently Willy B. *et al.* reported three-component synthesis of 2,4-disubstituted benzo[b][1,5]thiazepines via coupling–addition–cyclocondensation sequence.[3] Nigam S. *et al.* reported the synthesis of 2,4-disubstituted benzo[b][1,4]thiazepine by the reaction of 1-(benzo[d][1,3]dioxol-5-yl)-3-phenylpropane-1,3-diones with *o*-aminothiophenol in pyridine.[4] Moreover, there are several procedures reported for the synthesis of 2,3-dihydro-substituted-benzo[b][1,4]thiazepine.[5] But, to the best of our knowledge synthesis of only 2-substituted benzo[b][1,4]thiazepine as well as steroid fused benzo[b][1,4]thiazepines are rare in the literature. In last decade, *β*-halo-vinylaldehydes have been used as a potential synthon for the synthesis of novel heterocycles.[6] As a part of our ongoing research on development of new methodology for the synthesis of novel heterocycles including heterosteroids,[7] herein, we report a simple and high yielding synthesis of steroid and nonsteroid fused benzo[b][1,4]thiazepine as well as 2-substituted benzo[b][1,4]thiazepine derivatives by palladium acetate catalyzed reaction of steroidal/nonsteroidal *β*-

bromovinylaldehydes and 2-aminothiophenols using DMF as the solvent under heating condition.

Table 1. Synthesis of benzo[b][1,4]thiazepine derivative **3a**[a]



1a + **2a** → **3a**

Entry	Pd catalyst (mol%)	Base	Solvent	Temp (^oC)	Yield of **3a** (%)[b]
1	$PdCl_2$ (10 mol%)	Na_2CO_3	DMSO	120	58
2	$Pd(OAc)_2$ (10 mol%)	Na_2CO_3	DMSO	120	70
3	$Pd(OAc)_2$ (10 mol%)	Na_2CO_3	DMF	120	78
4	$Pd(OAc)_2$ (10 mol%)	Na_2CO_3	CH_3CN	110	52
5	$Pd(OAc)_2$ (5 mol%)	Na_2CO_3	DMF	120	78
6	$Pd(OAc)_2$ (5 mol%)	K_2CO_3	DMF	120	75
7	$PdCl_2(PPh_3)_2$(10 mol%)	Na_2CO_3	DMF	120	56
8	-	Na_2CO_3	DMF	120	0
9	$Pd_2(dba)_3$ (10 mol%)	Na_2CO_3	DMF	120	27[c]
10	$Pd(OAc)_2$ (5 mol%)	Na_2CO_3	DMF	120 (MW)	61[d]

[a]All reactions were run with 10 mol% of the PPh_3 for 8 hours unless specified.
[b]Yield of the isolated product.
[c]Ligand PPh_3 was not used
[d]Reaction was run for 5 minutes under microwave irradiation (720 Watt, 14 bar)

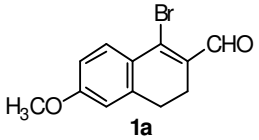
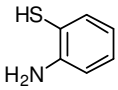
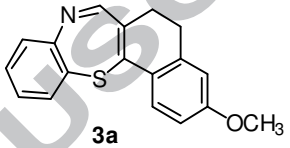
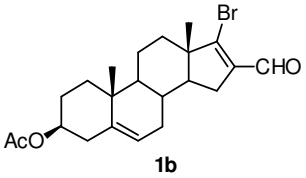
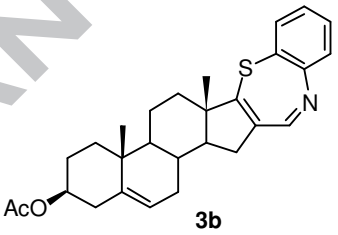
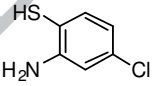
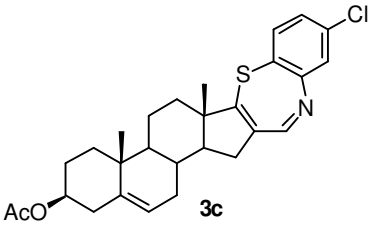
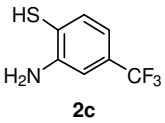
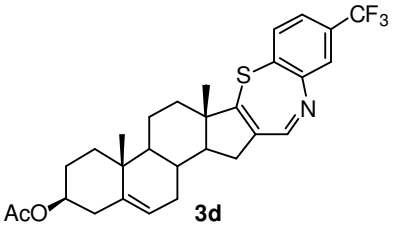
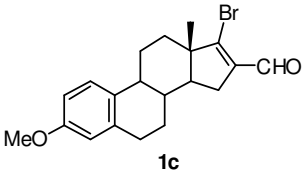
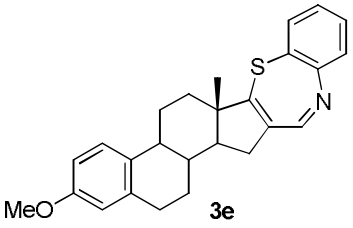
We started the synthesis of **3a** by the reaction of *β*-bromovinyl aldehyde **1a** (1 mmol), 2-aminothiophenol (**2a**, 1 mmol), palladium chloride (10 mol%), triphenylphosphine (10 mol%) and Na_2CO_3 (1.2 mmol) in dimethylsulfoxide. To our delight, after heating the reaction mixture for 8 hours at 120 ^oC, benzo[b][1,4]thiazepine derivative **3a** was obtained in 58% yield (entry 1, Table 1). This benzo[b][1,4]thiazepine derivative **3a** was fully characterized by ^1H NMR, ^{13}C NMR and mass spectroscopy. The ^1H NMR of compound **3a** exhibited a characteristic aromatic singlet signal at δ 8.77 (1H) for the thiazepine ring proton near to nitrogen atom. At the same time the ^1H NMR of this compound showed four doublet signals at δ 6.91 (J = 6.8 Hz, 1H), 7.88 (J = 9.0 Hz, 1H), 8.14 (J = 8.4 Hz, 1H), 8.42 (J = 8.4 Hz, 1H), two triplet signals at δ 7.51 (J = 7.5 Hz, 1H), 7.65 (J = 7.5 Hz, 1H) and one singlet signal at δ 6.92 for the benzene rings protons. The ^{13}C NMR spectrum of **3a** showed seventeen signals for carbons. The ESI mass spectra of compound **3a** exhibited $[M+1]^+$ molecular ion peak at m/z = 294 $[M+1]^+$. To determine the ideal

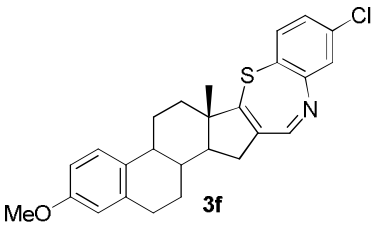
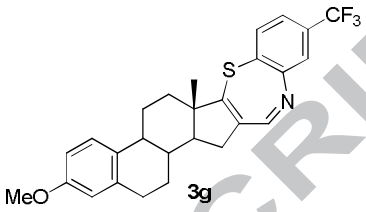
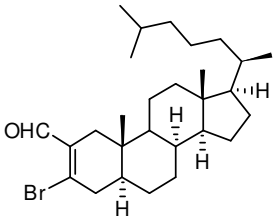
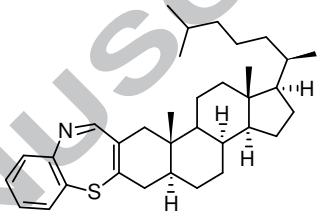
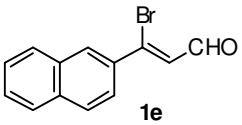
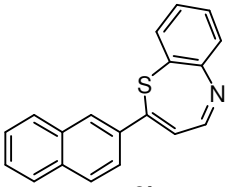
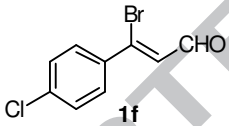
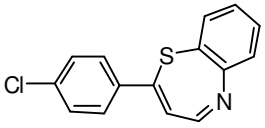
catalyst and solvent for the reaction we investigated this model reaction with some other palladium catalysts and solvents (Table 1). The yield of desired product **3a** increased to 70% and decreased to 56% when $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ were used respectively as the catalyst (entries 2 and 7, Table 1). Further investigation on the solvent, it was found that DMF was the most effective among the tested solvents and the yield of **3a** was increased to 78% (entry 3, Table 1), while there was sharp decrease in yield of **3a** to 52% (entry 4, Table 1) when acetonitrile was used. Then, we looked at the effect of catalyst loading on the yield of compound **3a** and we noticed that yield of **3a** remained same when the quantity of $Pd(OAc)_2$ was reduced to 5 mol% (entry 5, Table 1). The use of base K_2CO_3 in place of Na_2CO_3 decreased the yield of compound **3a** (entry 6, Table 1). In absence of Pd catalyst the reaction of **1a** and **2a** did not afford compound **3a**, instead it provided a complex mixture of products (entry 8, Table 1). Probably, in the absence of Pd catalyst and the presence of *ortho*-bromo group in the aldehyde **1a** facilitated side reactions such as coupling of amine group of **2a** with the vinyl halide **1a**.[8b] In absence of the ligand PPh_3, the $Pd(OAc)_2$ catalyzed reaction of **1a** and **2a** under heating condition (120 ^oC, 8 h) afforded low yield of the compound **3a** (33%) in dimethylsulfoxide (data not shown in Table 1). Use of phosphine-free palladium-catalyst such as $Pd_2(dba)_3$ (10 mol%) afforded poor yield of the product **3a** (27%) (entry 9, Table 1). Further, we studied the influence of microwave irradiation on the reaction of **1a** (1 mmol) and **2a** (1 mmol) in presence of 5 mol% $Pd(OAc)_2$, 10 mol% of PPh_3, and Na_2CO_3 (2.0 mmol) using the best solvent DMF. A substantial decrease in yield of **3a** (61%) along with the formation of complex mixture of products was observed in 5 minutes of reaction time (entry 10, Table 1).

With the optimized reaction condition in hand (entry 5, Table 1), the D-ring steroidal β-bromovinyl aldehydes (**1b**-**c**) were tested under this condition with different substituted 2-aminothiophenols (**2a**-**c**) to afford new benzo[b][1,4]thiazepine fused steroidal derivatives **3b**-**g** in 69-77% yields (entry 2-7, Table 2). Similarly, A-ring steroidal β-bromovinyl aldehyde **1d**

reacted with 2-aminothiophenol (**2a**) to afford benzo[b][1,4]thiazepine fused steroidal derivative **3h** in 70% yield (entry 8, Table 2). Moreover, nonsteroidal *β*-bromovinyl aldehydes such as **1e** and **1f** reacted with 2-aminothiophenol (**2a**) to afford 2-substituted benzo[b][1,4]thiazepines in 72-76% yields (entry 9-10, Table 2). The known starting *β*-bromoformyl compounds **1a**-**f** were synthesized following known procedure.[8]

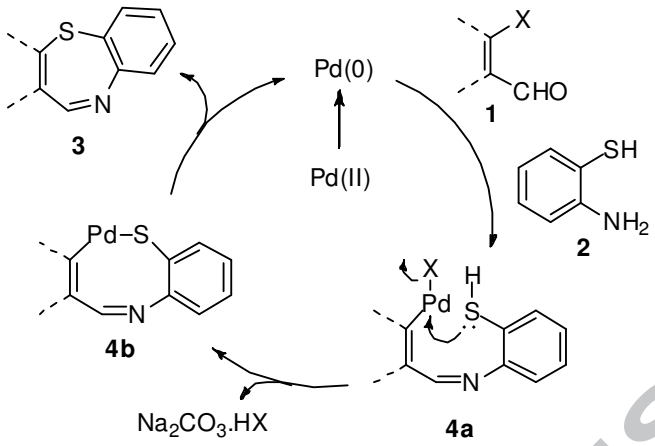
Table 2. $Pd(OAc)_2$ catalyzed synthesis of benzo[*b*][1,4]thiazepine

Entry	*β*-Bromovinyl aldehyde	Aminothiophenol	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	78
2	 **1b**	**2a**	 **3b**	72
3	**1b**	 **2b**	 **3c**	69
4	**1b**	 **2c**	 **3d**	74
5	 **1c**	**2a**	 **3e**	77

6	**1c**	**2b**	 **3f**	75
7	**1c**	**2c**	 **3g**	76
8	 **1d**	**2a**	 **3h**	70
9	 **1e**	**2a**	 **3i**	76
10	 **1f**	**2a**	 **3j**	72

[a]Yield of the isolated product.

We proposed a plausible mechanism for this palladium catalyzed cyclization reaction which is shown in Scheme 1. Oxidative addition of the vinylic halide group of **1** to Pd(0) and the reaction of aldehyde group of **1** with arylamine produces an organopalladium imine intermediate **4a**. Intramolecular reaction of vinylic palladium with the thiol group of intermediate **4a** produces an eight-membered palladacyclic intermediate **4b** which on subsequent reductive elimination produces compound **3** and regenerates Pd(0).



Scheme 1. Plausible mechanism of Pd-mediated formation of compound **3**

In conclusion, a simple and efficient reaction for the synthesis of steroid/nonsteroid fused benzo[b][1,4]thiazepines and 2-arylsubstituted benzo[b][1,4]thiazepines was developed using $Pd(OAc)_2$ as the catalyst in DMF solvent under heating condition. A wide variety of steroidal/nonsteroidal β-bromovinyl aldehydes and 2-aminothiophenols undergo this reaction to give good yields of benzo[b][1,4]thiazepine derivatives.

Acknowledgements

We are grateful to Director, CSIR-NEIST for his keen interests. This work was financially supported by CSIR-OSDD (HCP-0001), CSIR-ACT (CSC0301) and CSIR-ORIGIN (CSC 0108) projects.

Supplementary Material

Supplementary data (general experimental procedure, characterization data, ^{1}H NMR and ^{13}C NMR spectra for all compounds) associated with this article can be found, in the online version, at http://.....

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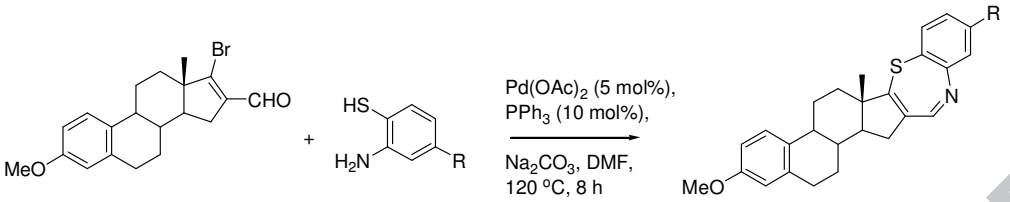
Graphical Abstract



(10 examples of steroidal and nonsteroidal 1,5-benzothiazepines, 69-78%)