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Catalysis by zeolite leading to the construction of thiazole ring: an improved synthesis of 4-alkynyl substituted thiazoles

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ABSTRACT

Zeolite H-beta facilitated the reaction of α-chloro acetyl chloride with 1,2-bis-trimethyl silyl acetylene to give 1-chloro-4-(trimethylsilyl)but-3-yn-2-one which on treatment with thioacetamide afforded 2-methyl-4-[(trimethylsilyl)ethynyl]thiazole. L-Proline on the other hand facilitated the coupling reaction of 2-methyl-4-[(trimethylsilyl)ethynyl]thiazole with (hetero)aryl halides (modified Sonogashira reaction) under Pd-Cu catalysis in the presence of aqueous K_2CO_3 affording an improved method for the synthesis of corresponding 4-alkynyl substituted thiazole derivatives.

The thiazole framework has been found to be an integral part of many natural products as well as various pharmacologically active substances.[1] For example, thiazole derivatives have been used for the treatment of various CNS related sufferings[2–12] such as pain,[2] depression,[3–10] anxiety,[12] etc. Several 4-alkynyl substituted thiazole derivatives such as 2-methyl-4-(pyridin-3-ylethynyl)thiazole (**A**) and 2-methyl-4-(phenylethynyl)thiazole (**B**) (Fig. 1) have been reported as potent and selective metabotropic glutamate subtype 5 receptor antagonists with anxiolytic activity[12] whereas compound **C** (or [18F]SP203, Fig. 1) was found to be effective as a positron emission tomography (PET) radio ligand in rhesus monkeys.[13]

The strategy used for the synthesis of 4-alkynyl substituted thiazole derivatives generally involved a Sonogashira-type coupling of appropriate aryl or heteroaryl halides with 4-(trimethylsilylethynyl)-substituted-1,3-thiazole (Scheme 1)[12,14] which in turn had been prepared via the reaction of α-chloro acetyl chloride with bis-trimethyl silyl acetylene in the presence of $AlCl_3$ followed by treating the resulting ynone with thioacetamide. While this strategy has been used successfully for the preparation of a number of compounds earlier, the requirement of a stoichiometric quantity of environmentally harmful and non-recyclable $AlCl_3$ during the generation of the 1,3-thiazole ring precursor was one of the major drawbacks of this procedure. Additionally, the yields of coupled alkynes obtained via the Sonogashira type coupling at 70–80 °C were not particularly high in all cases. This prompted us to develop an improved method for the synthesis of 4-alkynyl substituted thiazole derivatives in good yields. Herein we report the first use of zeolite H-beta followed by thioacetamide for the construction of 1,3-thiazole ring and subsequent Sonogashira type coupling in the presence of L-proline under mild conditions (Scheme 1).

The use of solid supports such as zeolites[15] has been explored in various organic reactions because of several advantages such as their acidic properties, shape-selectivities, environmental friendly nature along with easy work-up, the high purity of products, and recycling of the catalysts. Thus, zeolite H-beta has been reported to be an efficient catalyst in a number of chemical transformations including alkylation[16] and acylation.[17] Its activity owes to its large pore size, high Si/Al ratio, high acid strength, and thermal stability. In view of its role similar to $AlCl_3$ in a Friedel–Crafts acylation of anisole using acetyl chloride[18] we anticipated that like $AlCl_3$ the zeolite H-beta might facilitate the reaction of α-chloro acetyl

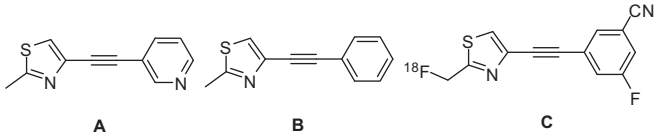

Figure 1. Pharmacologically active 4-alkynyl substituted thiazole derivatives.

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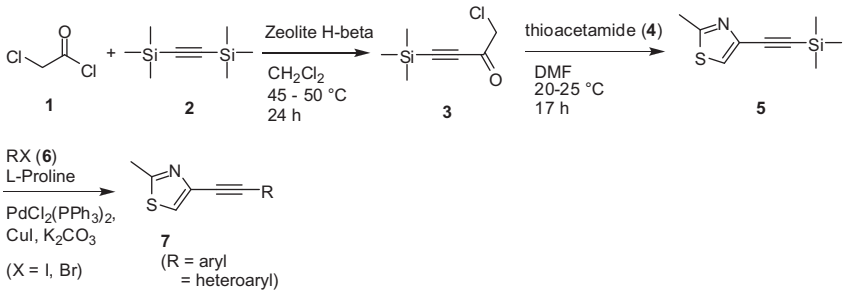
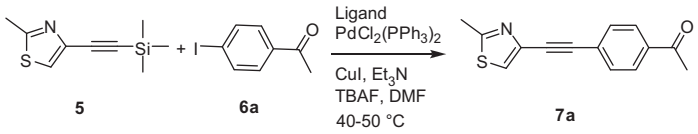


Scheme 1. Zeolite H-beta mediated construction of 1,3-thiazole ring and subsequent Sonogashira-type alkynylation in the presence of L-proline.

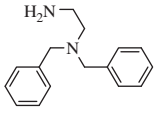
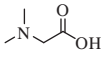
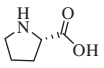
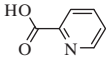
chloride (**1**) with 1,2-bis-trimethyl silyl acetylene (**2**). Initially, we examined the zeolite H-beta mediated reaction of **1** with **2** in dichloromethane (DCM) at room temperature when the formation of desired product that is 1-chloro-4-(trimethylsilyl)but-3-yn-2-one (**3**, Scheme 1) was not observed after 48 h. The increase of reaction temperature to 40–45 °C however afforded the expected product **3** (~70% yield) and the reaction was completed within 24 h. To test the recyclability of the catalyst the zeolite H-beta was separated from the reaction mixture by filtration, washed with DCM, dried, and reused. This process was repeated twice when the product **3** was isolated in 65% and 60% yields. While a marginal drop in product yield was observed in these cases the catalyst however can potentially be recycled. Nevertheless, we were delighted to develop an alternative but an environmentally safer method for the synthesis of compound **3** which was then used for the construction of the thiazole ring. The reaction of compound **3** with thioacetamide (**4**) in DMF provided the desired 2-methyl-4-[(trimethylsilyl)ethynyl]thiazole **5** in good yield (60% yield) (Scheme 1).

Having the key compound **5** in hand we then examined the one-pot modified Sonogashira coupling of **5** which involved an in situ desilylation in the presence of tetrabutylammonium fluoride (TBAF) followed by Pd-Cu mediated cross-coupling of the resulting terminal alkyne generated with an appropriate aryl halide. Accordingly, the reaction of **5** with 1-(4-iodophenyl)ethanone (**6a**) was carried out under the conditions (e.g., $Pd(PPh_3)_4$, CuI, NEt_3, TBAF in DMF at 80 °C or $PdCl_2(PPh_3)_2$, PPh_3, CuI, NEt_3, TBAF, Bu_4NI in DMF at 80 °C) reported earlier.[12,14b] While the reaction proceeded in these cases the desired product that is 1-{4-[(2-methylthiazol-4-yl)ethynyl]phenyl}ethanone (**7a**) however was isolated only in 30–40% yield due to the formation of side product caused by the oxidative homocoupling[19] (Glaser coupling) of the terminal alkyne generated in situ. The yield of **7a** could not be improved in spite of our several attempts. Since CuI in the presence of amine base plays a significant role in such homocoupling reaction, in order to increase the product yield we decided to examine the effect of a range of ligands (**L1–L6**) on the present coupling reaction. The ligands were chosen based on their potential ability to chelate a copper salt thereby modulating its reactivity. The results of this study

Table 1
Effect of ligands on modified Sonogashira coupling of **5** with **6a**[a]

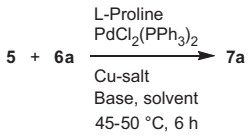


5 **6a** **7a**

Entry	Ligand	Time (h)	Yield[b] (%)
1	 **L1**	12	30
2	 **L2**	24	10
3	 **L3**	6	85
4	 **L4**	24	10
5	 **L5**	24	15
6	 **L6**	24	10

[a] All the reactions were carried out by using **5** (5.11 mmol, 1.0 equiv), **6a** (5.63 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (0.042 mmol), ligand (0.51 mmol), CuI (0.25 mmol), triethylamine (6.39 mmol, 1.25 equiv), and TBAF (5.63 mmol, 1.1 equiv) in DMF (2.5 mL).
[b] Isolated yields.

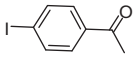
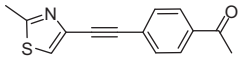
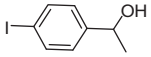
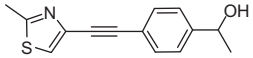
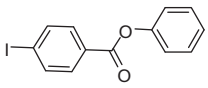
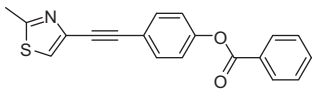
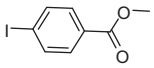
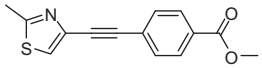
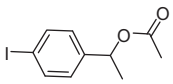
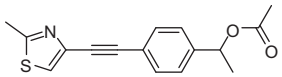
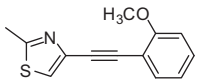
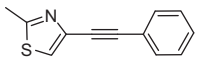
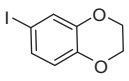
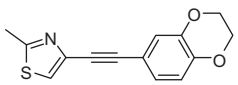
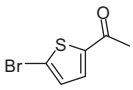
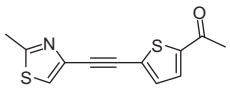
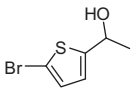
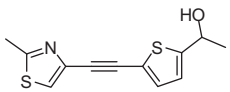
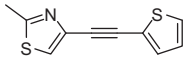
Table 2
Effect of Cu salts, solvents, and bases for Sonogashira coupling reaction



Entry	Cu-salt	Base	Solvent	Yield[b] (%)
1	CuI	K_2CO_3	DMF	80
2	CuI	Cs_2CO_3	DMF	55
3	CuI	DIPA	DMF	47
4	CuI	Et_3N	DMF	65
5	CuI	K_2CO_3	Toluene	30
6	CuI	K_2CO_3	*i*-PrOH	60
7	CuBr	K_2CO_3	DMF	35
8	Cu_2O	K_2CO_3	DMF	0
9	$Cu(OAc)_2$	K_2CO_3	DMF	15
10	CuI	K_2CO_3	DMF–H_2O	85

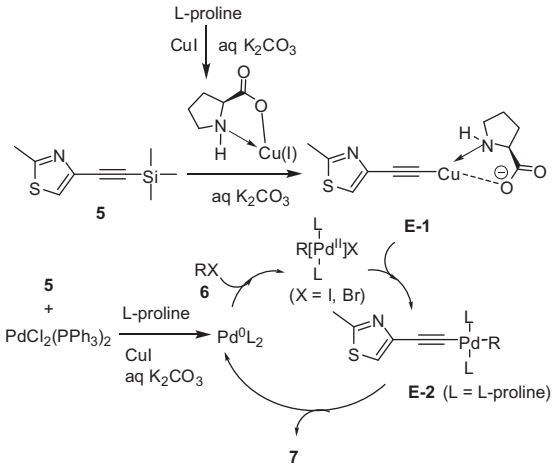
[a] All the reactions were carried out by using **5** (5.11 mmol, 1.0 equiv), **6a** (5.63 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (0.042 mmol), L-proline (0.51 mmol), Cu-salt (0.25 mmol), and a base (6.24 mmol, 1.25 equiv) in a solvent (2.5 mL) at 45–50 °C.
[b] Isolated yields.

Table 3
Pd-Cu mediated coupling reaction of 2-methyl-4-(trimethylsilylethynyl)-thiazole (**5**) with aryl and heteroaryl halides (**6**) in the presence of L-proline[a]

Entry	Aryl/heteroaryl halide (**6**)	Product[b] (**7**)	Time (h)	Yield[c] (%)
1	 **6a**	 **7a**	6	85
2	 **6b**	 **7b**	8	70
3	 **6c**	 **7c**	3	85
4	 **6d**	 **7d**	6	85
5	 **6e**	 **7e**	5	75
6	 **6f**	 **7f**	3	60
7	 **6g**	 **7g**	6	75
8	 **6h**	 **7h**	5	85
9	 **6i**	 **7i**	5	60
10	 **6j**	 **7j**	5	55
11	 **6k**	 **7k**	3	70

[a] All the reactions were carried out by using **5** (5.11 mmol, 1.0 equiv), **6** (5.63 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (0.042 mmol), L-proline (0.51 mmol), CuI (0.25 mmol), K_2CO_3 (6.24 mmol, 1.25 equiv) in DMF (2.5 mL), and water (0.15 mL) at 45–50 °C.
[b] Identified by ^1H NMR, IR, and MS.
[c] Isolated yields.

are summarized in Table 1. The reaction was initially performed in the presence of 10 mol % of N^1,N^1-dibenzyl-1,2-ethanediamine (**L1**) in DMF for 12 h when no improvement of product yield was observed (Table 1, entry 1). The use of 2-(dimethylamino)acetic acid (**L2**) was also found to be ineffective (Table 1, entry 2). The yield of **7a** however was improved significantly when L-proline (**L3**) was used as a ligand and the reaction was completed within 6 h (Table 1, entry 3). The oxidative homocoupling of alkyne was suppressed considerably though not completely in this case leading to the formation of a purer product. To suppress the homocoupling of alkyne completely, we tried a few other ligands for example **L4–6** but our effort was not successful (Table 1, entries 4–6). Having identified L-proline as the best among the ligands tested, we then examined the coupling reaction of **5** with **6a** under various conditions for example by changing several parameters such as solvent, copper salt, and the desilylating agent (Table 2).



Scheme 2. Proposed reaction mechanism for the modified Sonogashira coupling of **5** with **6** in the presence of L-proline.

The use of K_2CO_3 in place of Et_3N and TBAF was found to be effective as the desired product **7a** was isolated in 80% yield (Table 2, entry 1). The use of other bases, such as Cs_2CO_3, diisopropyl ethyl amine (DIPA), or Et_3N decreased the product yield (Table 2, entries 2–4). Changing the solvent from DMF to toluene (Table 2, entry 5) or *i*-PrOH (Table 2, entry 6) or the copper catalyst from CuI to CuBr (Table 2, entry 7) or Cu_2O (Table 2, entry 8) or $Cu(OAc)_2$ (Table 2, entry 9) did not provide good yield of **7a**. Interestingly, the use of water as a co-solvent though did not improve the product yield, afforded a much purer product (Table 2, entry 10) perhaps due to the enhanced solubility of K_2CO_3 in the aqueous reaction medium. Thus, the combination of L-proline, $(PPh_3)_2PdCl_2$, CuI, and K_2CO_3 in H_2O–DMF was found to be the best among all the conditions tested. A variety of aryl iodides (**6**) were coupled with **5** under this condition to afford the corresponding 4-alkynyl substituted thiazole derivatives (**7**) in good yields (Table 3).[20] The presence of carbonyl, hydroxyalkyl, acyloxyalkyl, ester, or ether substituents on the aromatic ring of **6** was well tolerated and the reaction proceeded smoothly in all these cases. The reaction also proceeded well when 2-bromothiophene derivatives were employed.

The mechanism of the Pd-Cu mediated coupling of **5** with **6** can be envisaged as shown in Scheme 2. The reaction seems to proceed via desilylation[21] of compound **5** in the presence of aqueous K_2CO_3 which subsequently forms the corresponding copper acetylide (**E-1**) via reacting with L-proline chelated Cu(I) species.[22] The intermediate **E-1** then undergoes *trans*-metallation with the organo palladium complex RPd(II)X generated from RX and the Pd(0) species produced in situ to give intermediate **E-2**. It is evident from entry 3 (vs other entries) of Table 1 and entry 10 (vs other entries) of Table 2 that L-proline in the presence of aqueous K_2CO_3 played a favorable role in generating Pd(0) species in situ.[23] The intermediate **E-2** on reductive elimination of Pd(0) provided the expected product **7** along with the Pd(0) species to complete the catalytic cycle. The observed suppression of oxidative homocoupling reaction could be explained by the chelating effect of L-proline which perhaps prevented the copper acetylide to participate in the homocoupling reaction thereby diminishing the formation of undesired side product.

In conclusion, zeolite H-beta facilitated the reaction of α-chloro acetyl chloride with 1,2-bis-trimethyl silyl acetylene to give 1-chloro-4-(trimethylsilyl)but-3-yn-2-one which on treatment with thioacetamide afforded 2-methyl-4-[(trimethylsilyl)ethynyl]thiazole. In comparison to the previously reported $AlCl_3$ mediated method, the present process represents a useful but relatively safer alternative where the zeolite H-beta used can potentially be recycled. L-Proline on the other hand facilitated the coupling reaction of 2-methyl-4-[(trimethylsilyl)ethynyl]thiazole with (hetero)aryl halides (modified Sonogashira reaction) under Pd-Cu catalysis in the presence of aqueous K_2CO_3 affording an improved method for the synthesis of corresponding 4-alkynyl substituted thiazole derivatives. A variety of (hetero)aryl iodides and bromides possessing carbonyl, hydroxyalkyl, acyloxyalkyl, ester, or ether substituents were employed to give the coupled products in good yields. The overall process may find uses in the generation of libraries of small molecules of potential pharmacological interest based on 4-alkynyl substituted thiazole.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.062.

References and notes

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20. (a) *Preparation of compound* ***5****; Step 1*: To a solution of bis (trimethylsilyl)acetylene (15.7 mL, 70.0 mmol) and chloroacetyl chloride (5.6 mL, 70.0 mmol) in CH_2Cl_2 (120 mL), was added Zeolite H-beta (9.00 g). The mixture was stirred at 45–50 °C for 24 h. After completion of the reaction (monitored by TLC) the mixture was cooled to room temp and filtered to separate the catalyst. The filtrate was collected and concentrated. The residue was treated with ethyl acetate (75 mL) and washed with cold water (2 × 25 mL). The organic layers were collected, combined, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give the desired 1-chloro-4-(trimethylsilyl)but-3-yn-2-one (**3**) (8.10 g, 70% yield) which was used directly in the next step. *Step 2*: To a solution of compound **3** in DMF (120 mL) was added thioacetamide (6.31 g, 84.0 mmol) and the mixture was allowed to stir at 20–25 °C for 17 h. After completion of the reaction (indicated by TLC) the mixture was diluted with EtOAc (100 mL), washed with 0.1 N HCl (300 mL) and H_2O (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under low vacuum. The residue was purified by column chromatography on silica gel using hexanes–EtOAc to give the desired product **5** (7.11 g, 60% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.27 (s, 9H), 2.70 (s, 3H), 7.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 10.34 19.16, 83.36, 94.43, 98.28, 122.91, 122.89, 136.84, 165.46; MS (ESI) *m*/*z* 196.10 $(M+H)^+$; IR (cm^{-1}, KBr) 2163.20.; HRMS (ESI) calcd for $C_9H_{14}NS$ $(M+H)^+$ 196.0616, found 196.0611. (b) *General procedure for the preparation of compound* ***7***: To a solution of 2-methyl-4-(trimethylsilylethynyl)-thiazole (**5,** 5.11 mmol) in DMF (2.5 mL) was added an appropriate (hetero)aryl halide (**6**, 5.63 mmol, 1.1 equiv) under nitrogen. To this mixture were added $PdCl_2(PPh_3)_2$ (0.042 mmol, 0.01 equiv), L-proline (0.51 mmol, 0.1 equiv), CuI (0.25 mmol, 0.05 equiv), K_2CO_3 (6.24 mmol, 1.25 equiv), and water (0.15 mL). The mixture was stirred at 45–50 °C for the time mentioned in Table 3. After completion of the reaction the mixture was cooled to room temp, partitioned between EtOAc (10 mL) and 0.1 N HCl (3.0 mL). The organic layer was collected, washed with cold water (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under low vacuum. The residue was purified by column chromatography on silica gel using hexane–EtOAc as solvent system to give the desired product; compound **7a**: Pale yellow solid; mp 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 2.75 (s, 3H), 7.43 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 26.6, 86.5, 87.9, 123.1, 127.3, 128.2 (2C), 131.8 (2C), 136.4, 142.0, 165.9, 197.2; IR (cm^{-1}, KBr) 2210, 1678; *m*/*z* (CI) 242 (M+1, 100%); HRMS (ESI) calcd for $C_{14}H_{12}NOS$ $(M+H)^+$ 242.0640, found 242.0645. compound **7b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, 3H) 2.74 (s, 3H), 4.94 (q, *J* = 6.4 Hz, 1H), 7.35 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 25.1, 65.4, 70.0, 71.3, 121.5, 122.1, 125.4 (2C), 131.9 (2C), 138.3, 146.3, 166.6; IR (cm^{-1}, KBr) 3383, 2216, 1735; *m*/*z* (CI) 244 (M+1, 100%); HRMS (ESI) calcd for $C_{14}H_{14}NOS$ $(M+H)^+$ 244.0796, found 244.0814.
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