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L-Proline promoted cross-coupling of vinyl bromide with thiols catalyzed by CuBr in ionic liquid

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Abstract—A method for the synthesis of vinyl sulfides by the coupling of vinyl bromides with thiols using the copper(I) bromide as catalyst and L-proline as ligand was reported. The best yields were obtained in the ionic liquid [Bmim]BF_4 with the retention of stereochemistry. This protocol is palladium-free, tolerates both aromatic and aliphatic thiols, possesses good selectivity between alcohol and thiol, and does not require the use of expensive or air-sensitive additives.

Alkenyl sulfides are important synthetic intermediates in organic synthesis. They are equivalents of carbonyl compounds,[1] and readily transformed to sulfoxides and sulfones,[2] etc. Sulfur may be also used as an auxiliary functional group in synthetic sequences as it can activate the C–H bond, facilitate the loss of the α-hydrogen atom and stabilize the carbon anion, cation or radicals thus formed.[3] Also there are some other uses for the alkenyl sulfides.[4] Various methods for their syntheses have been explored. Among them the addition of thiols to alkynes by free radical conditions or by anionic addition conditions is one of the most straightforward methods to obtain vinyl sulfides, affording the anti-Markovnikov product, usually as a stereoisomeric mixture.[5] Another noteworthy methodology to add thiols to alkynes is the addition catalyzed by transition metals (Pd, Pt, Rh, Ru, etc.) complex.[6] The third valuable protocol to gain the vinyl sulfides is the cross-coupling of thiols with the alkenyl halide under the catalysis of transition metal complex in a stereospecific manner. The first example was reported by Murahashi and co-workers in 1979, they coupled (*Z*)- and (*E*)-β-bromostyrene with lithium or sodium benzenethiolates using $Pd(PPh_3)_4$ as catalyst.[7] However, since then few reports have appeared in the literature for the formation of vinyl sulfur bonds by cross-coupling of vinyl halides with thiols using transition metal catalysts. Recently, Venkataraman reported a copper-catalyzed synthesis of vinyl sulfides via coupling reaction, but with vinyl iodides as substrates.[8]

On the other hand, ionic liquids as the novel 'solutions' for transition metal catalysis have been extensively studied in recent years.[9] Various metal-catalyzed reactions, including copper-catalyzed Ullmann-type reaction,[10] and copper–proline-catalyzed formation of C–N,[11] have been demonstrated in ionic liquids(IL) and excellent results have been obtained.

Here we wish to report a cross-coupling of vinyl bromides with thiols catalyzed by CuBr–proline in ionic liquid. Firstly, we explored the coupling by the reaction of β-bromostyrene with *p*-methylthiophenol catalyzed by 10 mol % CuI and 20 mol % L-proline in IL [bmim]BF_4 (bmim: 1-butyl-3-methyl imidazolium) at 110 °C in the presence of K_2CO_3. The reaction proceeded well and the vinyl sulfide was obtained in good yield, and a little higher yield was observed when CuBr was used as a catalyst (Table 1, entries 4 and 7). CuCl was also tested and it was not very effective (Table 1, entry 8). The reaction is very slow if the reaction temperature is below 90 °C (Table 1, entries 5 and 6). We also examined the effects of some common organic solvents. Acetonitrile was ineffective for the coupling, probably due to the low boiling point; both DMF and DMSO were effective, but the best yield was obtained from ionic liquid [bmim]BF_4. Also we screened several bases including K_2CO_3, KOH, K_3PO_4 and NaOH and finally

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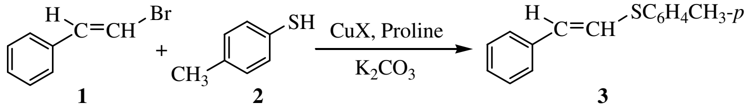
Table 1. Effects of CuX, temperature and solvents on the coupling of β-bromostyrene with *p*-methylthiophenol



Entry	Solvent	CuX	React. temp (°C)	React. time (h)	Yield (%)[a]
1	CH_3CN	CuBr	Reflux	48	0
2	DMF	CuBr	110	17	70
3	DMSO	CuBr	110	17	78
4	[Bmim]BF_4	CuBr	110	6	96
5	[Bmim]BF_4	CuBr	90	6	12
6	[Bmim]BF_4	CuBr	90	12	30
7	[Bmim]BF_4	CuI	110	6	80
8	[Bmim]BF_4	CuCl	110	15	33

CuX: 10 mol %; L-proline: 20 mol %; K_2CO_3: 4 mmol; vinyl bromide 2 mmol; thiol 2.2 mmol; ionic liq. 4 mL.

[a] Isolated yield.

we found that K_2CO_3 is the best base in the coupling of bromostyrene with thiophenols.

The amino acids were found to be the very effective ligands in the coupling reactions catalyzed by CuX recently.[11,12] In this reaction, we also used L-proline as an additive. Some other amino acids were also screened and proven effective, but the best yield was obtained with L-proline (Table 2, entry 1). If no amino acid was added, almost no coupling product was produced.

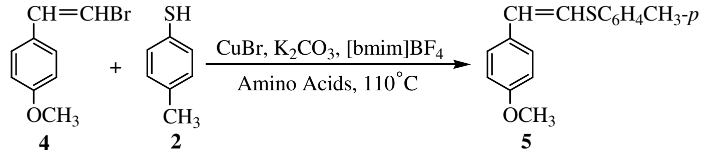
After the reaction condition was optimized, we started to explore the reaction scope with various vinyl bromides and thiols. The results are summarized in Table 3.

Vinyl bromide coupled to both aromatic and aliphatic thiols in good to excellent yields, although the longer reaction times were required for the aliphatic thiols (Table 3, entries 14, 15 and 16). Both electron-rich and electron-poor thiols were readily reacted with the vinyl bromide under this protocol. For 2-mercaptoethanol where both hydroxyl and thiol groups are present, the thiol group coupled preferentially with vinyl bromide and no cross-coupling between the vinyl bromide and the hydroxyl group was observed (Table 3, entries 14 and 15), therefore hydroxy-protection is not necessary. A good stereoselectivity was also observed, for example, when 4-methyl-β-bromostyrene is coupled with 4-isopropylthiophenol, the ratio of (*E*)-β-(isopropylphenylthio)-4-methylstyrene to (*Z*)-isomer was 94/6 (according to ^{1}H NMR spectra); for coupling of 4-methyl-β-bromostyrene with thiophenol the product ratio of (*E*)- to (*Z*)- is 94:6 (from ^{1}H NMR spectra).

Another advantage of this protocol is that the IL–proline–CuBr system can be reused after a simple treatment. Because the metal catalysts are immobilized in IL and the separation of products from reaction mixture by extraction will not remove the CuBr or proline or IL, the CuBr–proline–IL mixture was vacuumed after the product was separated, and could be re-used again with little efficiency decline in the first several runs (Table 4).

In summary, we have developed a mild, efficient and comparatively cheap methodology for the synthesis of vinyl sulfides by the coupling of vinyl bromide with thiols in a highly stereoselective manner using copper(I) bromide as catalyst and L-proline as ligand. The best yields were obtained in the ionic liquid [bmim]BF_4 with the retention of stereochemistry. This protocol is palladium-free, tolerates both aromatic and aliphatic thiols,

Table 2. The effect of different α-amino acids in the coupling of 4-methoxy-β-bromostyrene with 4-methylthiophenol



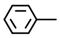
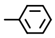
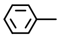
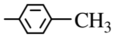
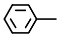
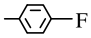
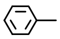
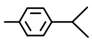
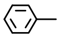
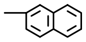
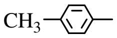
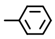
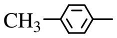
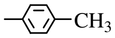
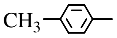
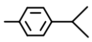
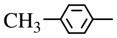
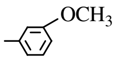
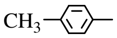
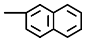
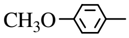
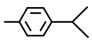
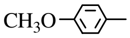
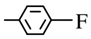
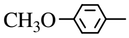
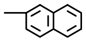
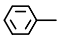
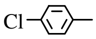
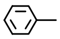
Entry	Amino acid	Time	Yield (%)[a]
1	L-Proline	6	92
2	Glycine	6	88
3	L-Analine	6	85
4	L-Histidine	6	76
5	L-Lysine	6	85
6	No	15	0

CuBr: 10 mol %; L-proline: 20 mol %; K_2CO_3: 4 mmol; vinyl bromide 2 mmol; thiol 2.2 mmol; ionic liq. 4 mL.

[a] Isolated yield.

Table 3. Copper-catalyzed cross-coupling of various aryl thiols with (*E*)-1-bromo-2-arylethene using the standard protocol

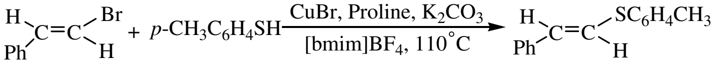
$$R_1{-}CH{=}CHBr + R_2SH \xrightarrow[\text{[bmim]BF}_4]{\text{CuBr, Proline, K}_2\text{CO}_3} R_1{-}CH{=}CH{-}SR_2$$

Entry	R_1	R_2	Temp (°C)	Time (h)	Yield (%)[a]	*E*:*Z*
1			110	6	88	87:13
2			110	6	96	95:5
3			110	6	90	90:10
4			110	6	95	92:8
5			110	6	92	93:7
6			120	8	88	94:6
7			120	8	85	86:14
8			120	8	96	94:6
9			120	8	82	91:9
10			120	8	75	98:2
11			110	6	91	98:2
12			110	6	92	95:5
13			110	6	88	91:9
14		$-CH_2CH_2OH$	110	10	83	94:6
15		$-CH_2CH_2OH$	110	10	90	95:5
16		$-CH_2Ph$	110	10	86	94:6

CuBr 10 mol %; L-proline 20 mol %; K_2CO_3 4 mmol; vinyl bromide 2 mmol; thiol 2.2 mmol; ionic liq. 4 mL.

[a] Isolated yield.

Table 4. Recycling of the IL–proline–CuBr system using the standard condition



$$\text{(H)(Ph)C=C(Br)(H)} + p\text{-}CH_3C_6H_4SH \xrightarrow[\text{[bmim]BF}_4,\ 110^\circ\text{C}]{\text{CuBr, Proline, K}_2\text{CO}_3} \text{(H)(Ph)C=C(SC}_6\text{H}_4\text{CH}_3\text{-}p\text{)(H)}$$

Run	1	2	3	4
Yield (%)	96	95	90	87

possesses good selectivity between hydroxyl and thiol, and does not require the use of expensive or air-sensitive additives. For the typical procedures and representative data please refer to Refs. 13 and 14.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.164.

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13. *Typical procedures*: To a mixture of β-bromostyrene (2 mmol, 0.37 g), CuBr (0.1 mmol, 0.015 g), L-proline (0.2 mmol, 0.023 g), K_2CO_3 (4 mmol, 0.4 g) and [Bmim]BF_4 (4 mL) in a 10 mL flask equipped with a magnetic stir bar, thiophenol (2.2 mmol, 0.24 g) was added. Under N_2 atmosphere, the mixture was stirred at 110 °C for 6 h. The resultant product was extracted by ethyl ether (3 × 2 mL). The product was further purified by column chromatography (10:1 petroleum ether/ethyl ether), yield: 0.37 g (88%).
14. *Representative data*: (*E*)-*β*-(*Phenylthio*)*styrene*:[8] Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.76$ (d, 1H, $J = 15.5$ Hz), 6.91 (d, 1H, $J = 15.5$ Hz), 7.25–7.46 (m, 10H); ^{13}C NMR (75 MHz): $\delta = 124.1$, 126.7, 127.6, 128.3, 129.4, 129.8, 130.5, 132.5, 135.9, 137.2 ppm; IR (KBr): $v = 3065$, 3022, 1582, 1477, 1439, 1066, 943, 784, 687 cm^{-1}.
    (*E*)-*β*-(*4′-Fluorophenylthio*)-*4-methoxystyrene*: mp 38–40 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.77$ (s, 3H), 6.64 (s, 2), 6.83 (d, 2H, $J = 8.8$ Hz), 7.00 (t, 2H, $J = 8.7$ Hz), 7.25 (d, 2H, $J = 8.8$ Hz), 7.33–7.41 (m, 2H); ^{13}C NMR (75 MHz): $\delta = 55.3$, 114.2, 114.3, 116.3 (d, $J = 21.9$ Hz), 120.6, 127.4, 129.3, 132.0 (d, $J = 8.1$ Hz), 132.3, 136.6, 159.5, 162.2 (d, $J = 245.3$ Hz) ppm; IR (KBr): $v = 3017$, 2846, 1606, 1510, 1489, 1468, 954, 800, 825, 630 cm^{-1}. Anal. Calcd for $C_{15}H_{13}FOS$: C, 69.21; H, 5.03. Found: C 69.50; H 4.93.