



Csp³-tellurium copper cross-coupling: synthesis of alkynyl tellurides a novel class of antidepressive-like compounds

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ABSTRACT

We present here the results on the synthesis of functionalized alkynyl tellurides using the reaction of vinyl, alkynyl, and aryl tellurides with several alkynyl iodides catalyzed by copper iodide. The reaction proceeded cleanly under mild reaction conditions, at room temperature, in the absence of base and ligand giving alkynyl tellurides in acceptable yields. The obtained compounds **3a–c** and **3m–o** were screened for antidepressive-like activity using the tail suspension test (TST) in mice. Compounds **3a–c** and **3m–o** administered at 10 mg/kg by oral route produced a significant antidepressant-like effect on the TST in mice.

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1. Pharmacology

Depression is a common disorder with high lifetime rates. It is a major cause of disability, and causes death both by suicide and due to raised rates of physical disorders.¹ Because the mechanism of depression is quite complex, many currently available antidepressants have low rates of response and remission and even severe adverse-effects.^{2,3} For that reason, it is necessary to research and develop more effective antidepressant drugs. Organotellurium compounds have demonstrated pharmacological properties, such as antioxidant^{4–7} and chemoprotective,^{8–10} and display low acute toxicity in animals.^{6,7,11} Therefore, organotellurium compounds may be an important source of new antidepressant drugs. Following our longstanding interest in pharmacological properties of organochalcogens, the present study was undertaken to investigate whether alkynyl vinyl tellurides **3a–c** and **3m–o** present antidepressant-like effect, employing tail suspension test (TST) in mice.

2. Chemistry

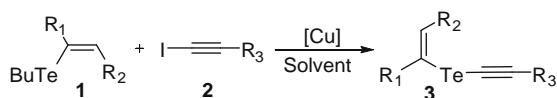
Great progress has been made in carbon-heteroatom bond formation via the cross-coupling reaction of heteroatom compounds using a copper-catalyzed system.¹² These improvements are certainly a consequence of the studies regarding the effects of sev-

eral ligands, such as aliphatic diamines, 1,10-phenanthroline, amino acids and their derivatives, and others. These important findings allow the use of common organic solvents (dichloromethane, chloroform, toluene, benzene, DMF, and DMSO) and weaker bases (K₂CO₃, Cs₂CO₃, and K₃PO₄), and they also allow the use of not only aryl iodide, but also aryl bromides and chlorides. After that, these reactions became more attractive and nowadays they can be carried out at lower temperatures, under milder conditions, and using a catalytic amount of the copper salts.

Chalcogenide compounds have found such wide utility because of their effects on an extraordinary number of very different reactions, including many carbon–carbon bond formations,¹³ under relatively mild reaction conditions. In addition, they have become attractive synthetic targets because of their chemo-, regio-, and stereoselective reactions,¹⁴ used in a wide variety of functional groups, thus avoiding protection group chemistry and useful biological activities.¹⁵ Among chalcogenides, vinylic tellurides are useful intermediates in organic synthesis.^{14d,16} Of the two isomers, the Z-vinylic tellurides have been employed more frequently as intermediates because of easy availability of these species.¹⁷ Lately, we have employed vinylic tellurides in the synthesis of natural products by using this cross-coupling reaction.¹⁸ To the best of our knowledge, the application of carbon–tellurium single bond in the copper cross-coupling has not been reported so far. In view of the lack of synthetic protocols using tellurides in this cross-coupling, there is a need for the development of a clear and mild procedure that is to be carried out at room temperature in the absence of a

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Scheme 1.

base and a ligand. Thus, our continuing interest in the organochalcogen chemistry as well as copper-catalyzed cross-coupling reactions prompted us to examine the cross-coupling reaction of vinyl, aryl, and alkynyl tellurides **1** with alkynyl iodides **2** to obtain a new class of tellurium compounds **3** (Scheme 1).

3. Results and discussion

The starting vinylic tellurides **1a–h**, **1j**, and **1k** were readily available by using the process of hydrotelluration of alkynes.¹⁹ The treatment of phenyllithium with elemental tellurium gave in situ the lithium tellurolate anion that was treated with 1-bromobutane to yield the telluride **1i**.²⁰ Finally, alkynyl tellurides **1l** and **1m** were obtained from reaction of alkynyl lithium derivatives with elemental tellurium followed by reaction with 1-bromobutane.²¹

With the starting materials in hand, our initial studies have focused on the development of an optimum set of reaction conditions. Hence, the coupling reaction of telluride **1a** (1 mmol) with alkynyl iodine **2a** (1.2 mmol) was treated with different copper catalysts under room temperature, in different solvents and in the presence and absence of additives, in order to optimize the reaction conditions.

As shown in Table 1, of the Cu(II) sources investigated, Cu(OAc)₂, CuCl₂, Cu(acac)₂, and Cu(OTf)₂ provided similar results giving the products in moderate yields: however, the use of CuBr₂ greatly increased the product yield (Table 1, entries 1–5). Cu₂O

Table 1
Optimization of reaction conditions for the formation of **3a**^a

Entry	Catalyst (mol %)	Solvent	Ligand	Yield (%) ^b
1	Cu(OAc) ₂ (10)	DMF	None	42
2	CuBr ₂ (10)	DMF	—	72
3	CuCl ₂ (10)	DMF	—	55
4	Cu(acac) ₂ (10)	DMF	—	43
5	Cu(OTf) ₂ (10)	DMF	—	42
6	Cu ₂ O nano(10)	DMF	—	42
7	CuCl(10)	DMF	—	69
8	CuBr(10)	DMF	—	55
9	CuI(10)	DMF	—	96
10	CuCN(10)	DMF	—	61
11	CuI(10)	DMSO	—	52
12	CuI(10)	EtOH	—	36
13	CuI(10)	MeCN	—	45
14	CuI(10)	THF	—	34
15	CuI(10)	Hexane	—	40
16	CuI(10)	DMF	1,10-Phen	86
17	CuI(10)	DMF	EDTA	42
18	CuI(10)	DMF	DMEDA	32
19	CuI(10)	DMF	TMEDA	75
20	CuI(10)	DMF	BiPy	—
21	CuI(1)	DMF	—	50
22	CuI(3)	DMF	—	65
23	CuI(5)	DMF	—	65

^a Reactions were performed in the presence of **1a** (1 mmol), **2a** (1.2 mmol) at room temperature for 6 h.

^b The yield was determined by GC.

nanoparticles also showed certain activity (Table 1, entry 6). With Cu(I) sources the yields varied from 55 to 96% (Table 1, entries 7–10). Since, using CuI (10 mol %) as catalyst the product was obtained in 96% yield, we considered CuI as the the best copper source for this catalytic system.

A series of approaches have shown that the use of ligands (such as aliphatic diamines, 1,10-phenanthroline, amino acids and their derivatives, and others) for copper catalysts resulted in numerous advantages.²² For this reason, in our experiment we also investigated the influence of some inexpensive ligands, such as 1,10-phenanthroline, EDTA, DMEDA, TMEDA, and bipyridine. As listed in Table 1, when the reaction was carried out using EDTA, DMEDA, and bipyridine the target product was not obtained (Table 1, entry 20) or was obtained in moderate yields (Table 1, entries 17 and 18), even though a long reaction time was used. The best ligands were 1,10-phenanthroline and TMEDA (Table 1, entries 16 and 19); however, the reaction was not improved compared to reaction carried out in the absence of ligand (Table 1, entry 9). Regarding the influence of the solvent in this cross-coupling reaction, optimal results were achieved using DMF (Table 1, entry 9). By using DMSO, EtOH, MeCN, THF, and hexane moderate yields were obtained (Table 1, entries 11–15). It is relevant to note that when the amount of catalyst is reduced from 10 to 1 mol %, a notable decrease in the yields was observed (Table 1, entries 21–23). In addition, no reaction occurred in the absence of copper catalyst even after 72 h.

Thus, the careful analysis of the optimized reactions revealed that the optimum conditions for this cross-coupling reaction procedure were the addition of telluride **1a** (1 mmol) and the appropriate alkynyl iodine **2a** (1.2 equiv) to a solution of CuI (10 mol %) in DMF (3 mL) at room temperature.²³

Using this condition, we were able to prepare alkynyl tellurides **3a** in 96% yield. To demonstrate the efficiency of this reaction, we explored the method by extending these conditions to other organotellurium compounds **1a–k** with different alkynyl iodines **2a–e**, and the results are summarized in Table 2.

First we explored the coupling of different vinyl tellurides; functionalized (**1a–g**, **1j**, and **1k**), nonfunctionalized (**1h**), and aryl tellurides (**1i**) gave the desired products in moderate to good isolated yields. Most importantly, the cross-coupling turned out to be general with respect to a diverse array of functionality in the electrophile sources. Satisfactorily, our experiments also showed that the reaction with electrophile sources having aryl, alkyl, and propargyl (**2a–e**) groups gave the product in acceptable yields. Finally, it is worth mentioning that through our methodology, it was possible to prepare highly functionalized organophosphorated alkynyl tellurides **3e'–f'** and **3g'**.

In view of the fact of occurrence of diene systems in many compounds with biological interest, we attempt to broaden the scope of our methodology performing the reaction using the alkynyl tellurides **1l** and **1m** and iodo alkynes to give symmetrical and unsymmetrical alkynyl tellurides **4**. It was found that the reaction worked well affording the desired coupling products in satisfactory yields. The results are summarized in Table 3.

Our working mechanism for the copper-catalyzed preparation of alkynyl tellurides is based on the following experimental data obtained: (1) in all cases we detected BuI as a side product; (2) the reaction works in the complete absence of reoxidant to change Cu(I)–Cu(0)–Cu(I); (3) no product was obtained when a sp²-carbon was bound to the tellurium atom in place of Bu group and; (4) no product was obtained using terminal alkynes in place of alkynyl iodide, then it could involve: (a) BuTe complexation with CuI; (b) insertion of CuI into the alkyne followed by nucleophilic attack of the tellurium atom on the copper to give the cationic organo-Cu(III) complex **a**;²⁴ (c) nucleophilic attack of iodide anion on the butyl group bound to the tellurium atom to give the Cu(III) inter-

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