

Stereoselective preparation of conjugated *E*-enynes from *E*-vinyl tellurides and terminal alkynes *via* Sonogashira cross-coupling†

Gilson Zeni,^{a*} Diego Alves,^a Jesus M. Pena,^a Antonio L. Braga,^a Helio A. Stefani^b and Cristina W. Nogueira^a

^a Departamento de Química, Laboratório de Bioquímica Toxicológica, UFSM, Santa Maria, RS, Brazil 97105-900. E-mail: gzeni@quimica.ufsm.br

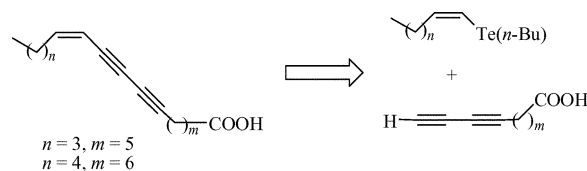
^b Faculdade de Ciências Farmacêuticas, USP, São Paulo, SP, Brazil

Received 23rd January 2004, Accepted 4th February 2004

First published as an Advance Article on the web 9th February 2004

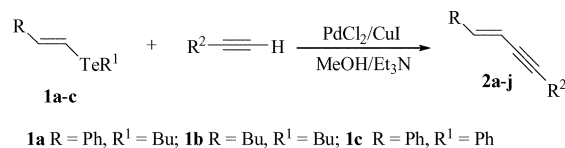
E-Vinyl tellurides undergo a direct cross-coupling reaction with terminal alkynes in the presence of palladium(II)/CuI in Et₃N at room temperature to give *E*-enynes in good yields. The methodology represents a general and efficient protocol for carrying out the synthesis of *E*-enynes under mild conditions with complete retention of configuration.

Vinyl tellurides are useful intermediates in organic synthesis.¹ Of the two isomers, the *Z*-vinyl tellurides have been employed more frequently as intermediates because of easy availability of these species.² One of the most important reactions of vinyl tellurides is their transmetalation.³ The vinyl organometallic obtained in this way can react with carbonyl compounds,⁴ α,β-unsaturated systems⁵ or epoxides.⁶ Lately, we have employed vinyl tellurides in the synthesis of polyacetylenic acids isolated from *Heisteria acuminata* by using a vinyl telluride cross-coupling reaction, Scheme 1.⁷



Scheme 1

Recently, new applications of vinyl tellurides utilizing palladium catalyzed cross-coupling have been described.⁸ In this case, they act as an equivalent of an aryl or vinyl carbocation. They react in a similar way to vinyl halides or triflates in the Sonogashira,⁹ Heck,¹⁰ Suzuki¹¹ and Stille¹² reactions. Our continuous efforts in the synthesis of enynes by cross-coupling reaction¹³ led us to find out that the *E*-vinyl tellurides **1a–c** can be effectively applied to the synthesis of *E*-enynes *via* a cross-coupling reaction with terminal alkynes, using palladium as catalyst, Scheme 2.¹⁴



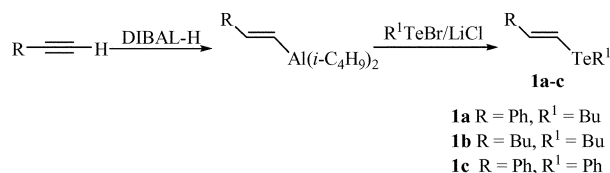
Scheme 2

The starting materials required for the coupling, *E*-vinyl tellurides **1a–c**, were synthesized by stereospecific *cis* hydroalumination of the acetylene,¹⁵ followed by transmetalation of the *E*-vinyl aluminate complexes formed with organotellurenyl bromide/LiCl¹⁶ (Scheme 3).

Table 1 Influence of the catalyst in the cross-coupling reaction

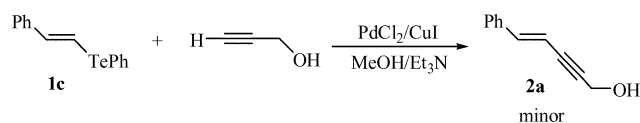
Entry	Catalyst (mol%)	Time (h)	Yield, 2a ^a (%)
1	Pd(PPh ₃) ₄ /CuI (20)	48	0
2	Pd(PPh ₃) ₄ (20)	48	0
3	PdCl ₂ /PPh ₃ (20)	20	8
4	PdCl ₂ (PPh ₃) ₂ (20)	20	5
5	Pd(OAc) ₂ (20)	24	2
6	PdCl ₂ (PhCN) ₂ (20)	20	5
7	PdCl ₂ /CuI (1)	24	23
8	PdCl ₂ /CuI (3)	24	30
9	PdCl ₂ /CuI (5)	24	47
10	PdCl ₂ /CuI (10)	12	62
11	PdCl ₂ /CuI (20)	3	76
12	PdCl ₂ (20)	24	28

^a All reactions were carried out with 1 mmol of *E*-vinyl tellurides **1a**, 2 mmol of 2-propyn-1-ol in methanol (5 mL) at room temperature in the presence of palladium catalyst and Et₃N (0.8 mL). Entries 1 and 7–11 used CuI.



Scheme 3

Our initial efforts were focused on the reactivity of *E*-vinyl telluride **1c** in the cross coupling reaction with 1-alkynes. Thus, **1c** (1 equiv.) was treated in methanol at room temperature with 2-propyn-1-ol (2 equiv.) in the presence of PdCl₂ (20 mol%)/CuI (20 mol%), and Et₃N (0.8 mL) as the base. Under these conditions, the corresponding enyne **2a** was obtained as a minor product, (Scheme 4). This may be explained by the possible transmetalation of Te with Pd at both the vinyl and aryl carbon giving undesirable homocoupling products.



Scheme 4

We tried reacting *E*-vinyl telluride **1c** in methanol at room temperature with 2-propyn-1-ol in the presence of PdCl₂ as catalyst, and Et₃N as base, in the absence of CuI. Under these conditions, the cross-coupling reaction still proceeded unsatisfactorily.

In view of these disappointing results, we decided to explore the reaction with the *E*-vinyl tellurides **1a** and **1b** under the same experimental conditions described above. In the course of the study, we found that the cross-coupling reaction of *E*-vinyl

† Electronic supplementary information (ESI) available: spectroscopic data for all new compounds as well as detailed experimental procedures. See <http://www.rsc.org/suppdata/ob/b4/b401059k/>

Table 2 *E*-Enynes **2** Prepared According to Scheme 2¹⁷

Entry	Telluride 1	<i>E</i> -Enyne 2	Time (h)	Yield (%)
1			3	76
2	1a		5	67
3	1a		6	68
4	1a		5	70
5	1a		6	75
6			3	78
7	1b		6	75
8	1b		5	64
9	1b		4	73
10	1b		3	70

tellurides **1a** and **1b** with 1-alkynes are best catalyzed by PdCl₂ (20 mol%)/CuI (20 mol% each) (entry 11; Table 1). Thus, the reaction of **1a** (1 equiv.) with 2-propyn-1-ol (2 equiv.) over 3 h in methanol at room temperature using PdCl₂/CuI (20 mol%) gave the *E*-enyne, in 76% yield. Other palladium complexes such as Pd(PPh₃)₄/CuI, Pd(PPh₃)₄, PdCl₂/PPh₃, PdCl₂(PPh₃)₂, Pd(OAc)₂, PdCl₂(PhCN)₂ were less effective (Table 1). The reaction was greatly enhanced by increasing the amount of catalyst from 1% to 20% (entries 7–11). A rather different trend was noted when the reaction was performed in the absence of copper salts, such as CuI, (entry 12; Table 1). This reaction is also highly affected by the solvent. The performance (yield of enyne) of various solvents in the same reaction under identical conditions decreased as follow [PdCl₂ (20 mol%)/CuI (20 mol%), rt, 3 h]: THF, acetonitrile, DMF (40–55%); pyridine, DME (22–35%); toluene, CH₂Cl₂, 1,2-dichloroethane, hexane (no cross-coupling product was observed).

The nature of the amine was critical for the success of the coupling. When different amines (piperidine, pyrrolidine, *n*-BuNH₂, Et₂NH, *i*-Pr₂NH) were used in lieu of Et₃N, unsatisfactory yields of the desired enynes were obtained. Careful analysis of the optimized reactions revealed that the optimum conditions for the coupling in Scheme 2 were found to be the

use of PdCl₂ (20 mol%)/CuI (20 mol%), MeOH (5 mL), (*E*)-vinyl telluride **1a** or **1b** (1 mmol), the appropriate alkyne (2 mmol) and Et₃N (0.8 mL) at 25 °C. Extending the coupling reaction to other alkynes, various *E*-enynes **2a–j** were obtained in good yields (Table 2).¹⁷

The formation of enynes was confirmed by the analysis of the ¹H NMR spectra. The stereoisomeric purities of the *E*-enynes **2a–j** were similar to starting *E*-vinyl tellurides **1a–b**,¹⁴ due to a complete retention of configuration in this type of reaction. The stereochemistry of the obtained enynes was easily established. As an example, the ¹H NMR spectrum of compound **2a**, showed a doublet at 6.8 ppm with a coupling constant of 16.3 Hz and a double triplet at 6.0 ppm with coupling constants of 16.3 Hz and 1.9 Hz. These coupling constants confirm the *trans* relationship of the hydrogen of the double bond.

In summary, we have explored the Pd(II) catalyzed cross-coupling reaction of *E*-vinyl tellurides with alkynes and established a new stereoselective route to *E*-enynes in good yields. The reaction proceeds cleanly under mild conditions. The cross coupling reaction was sensitive to the nature of the amine, catalyst and solvent. This novel approach to functionalized enynes could open a new route to the biologically important

enyne systems. The pharmacological activity of these compounds is under study in our laboratory.

Acknowledgements

We are grateful to the FAPERGS, CAPES, CNPq, UFSM and FAPESP (98/10821-0) for financial support. CNPq is also acknowledged for Ms (D. A.) fellowship.

Notes and references

- (a) J. V. Comasseto and R. E. Barrientos-Astigarraga, *Aldrichim. Acta*, 2000, **33**, 66–78; (b) J. V. Comasseto, L. W. Ling, N. Petragani and H. A. Stefani, *Synthesis*, 1997, **4**, 373–403; (c) N. Petragani, *Tellurium in Organic Synthesis*, Academic Press, London, 1994; (d) J. P. Marino and H. N. Nguyen, *J. Org. Chem.*, 2002, **67**, 6291–6296.
- (a) G. Zeni, H. B. Formiga and J. V. Comasseto, *Tetrahedron Lett.*, 2000, **41**, 1311–1313; (b) S. M. Barros, M. J. Dabdoub, V. B. Dabdoub and J. V. Comasseto, *Organometallics*, 1989, **8**, 1661–1665; (c) F. C. Tucci, A. Chieffi, J. V. Comasseto and J. P. Marino, *J. Org. Chem.*, 1996, **61**, 4975–4989.
- (a) A. Chieffi and J. V. Comasseto, *Synlett*, 1995, 671–674; (b) J. P. Marino, M. S. McClure, D. P. Holub, J. V. Comasseto and F. C. Tucci, *J. Am. Chem. Soc.*, 2002, **124**, 1664–1668.
- S. M. Barros, J. V. Comasseto and J. N. Barriel, *Tetrahedron Lett.*, 1989, **30**, 7353–7356.
- T. Hiroy, N. Kambe, A. Ogawa, N. Miyoshi, S. Murai and N. Sonoda, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1187–1188.
- J. P. Marino, F. C. Tucci and J. V. Comasseto, *Synlett*, 1993, 761–763.
- G. Zeni, R. B. Panatieri, E. Lissner, P. H. Menezes, A. L. Braga and H. A. Stefani, *Org. Lett.*, 2001, **3**, 819–821.
- (a) G. Zeni, A. L. Braga and H. A. Stefani, *Acc. Chem. Res.*, 2003, **36**, 731–738; (b) G. Zeni, C. W. Nogueira, D. O. Silva, P. H. Menezes, H. A. Stefani, A. L. Braga and J. B. T. Rocha, *Tetrahedron Lett.*, 2003, **44**, 685–688; (c) G. Zeni, C. W. Nogueira, J. M. Pena, C. Pilissao, P. H. Menezes, A. L. Braga and J. B. T. Rocha, *Synlett*, 2003, 579–581; (d) G. Zeni, C. W. Nogueira, D. O. Silva, P. H. Menezes, H. A. Stefani, A. L. Braga and J. B. T. Rocha, *Tetrahedron Lett.*, 2003, **44**, 1387–1390.
- (a) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467–4470; (b) E. Negishi and L. Anastasia, *Chem. Rev.*, 2003, **103**, 1979–2017.
- H. A. Dieck and F. R. Heck, *J. Organomet. Chem.*, 1975, **93**, 259–263.
- A. Suzuki, *Pure Appl. Chem.*, 1985, **57**, 1749–1758.
- W. J. Scott, M. R. Peña, K. Sward, S. J. Stoessel and J. K. Stille, *J. Org. Chem.*, 1985, **50**, 2302–2308.
- C. C. Silveira, A. L. Braga, A. S. Vieira and G. Zeni, *J. Org. Chem.*, 2003, **68**, 662–665.
- For additional examples of the preparation of *E*-enynes, see: (a) A. O. King, N. Okukado and E. I. Negishi, *J. Chem. Soc. Chem. Commun.*, 1977, **19**, 683–684; (b) H. P. Dang and G. Linstumelle, *Tetrahedron Lett.*, 1978, **13**, 191–194; (c) E. I. Negishi, T. Yoshida, A. Abramovitch, G. Lew and R. M. Williams, *Tetrahedron*, 1991, **47**, 343–356; (d) M. Alami and G. Linstumelle, *Tetrahedron Lett.*, 1991, **32**, 6109–6112; (e) M. Bujard, F. Ferri and M. Alami, *Tetrahedron Lett.*, 1998, **39**, 4243–4246; (f) M. Alami, F. Ferri and G. Linstumelle, *Tetrahedron Lett.*, 1993, **34**, 6403–6406.
- J. J. Eisch and C. Kaska, *J. Am. Chem. Soc.*, 1966, **88**, 2213–2215.
- M. J. Dabdoub and T. M. Cassol, *Tetrahedron*, 1995, **51**, 12971–12982.
- Typical procedure for the preparation of enynes 2:** To a two-necked 25 mL round-bottomed flask under an argon atmosphere containing PdCl₂ (0.036 g, 20 mol%), CuI (0.038 g, 20 mol%) and dry methanol (5 mL) was added *Z*-vinyl tellurides **1a** (0.287 g, 1 mmol). After stirring the mixture for 15 minutes at room temperature, 2-propyn-1-ol (0.112 g, 2 mmol) and Et₃N (0.8 mL) were added. The reaction was stirred at room temperature for 3 h. After this time the solid part was filtered under vacuum and the filtrate was treated with saturated brine and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography and eluted with hexane/ethyl acetate (80 : 20). **Selected spectral and analytical data for 2a:** (4*E*)-5-phenylpent-4-en-2-yn-1-ol: yield 0.120 g (76%); ¹H NMR: CDCl₃, 200 MHz, δ(ppm): 7.21–7.15 (m, 5H), 6.81 (d, *J* = 16.3 Hz; 1H), 6.00 (dt, *J* = 16.3 and 1.9 Hz; 1H), 4.32 (s; 2H), 2.45 (s, 1H); ¹³C NMR: CDCl₃, 50 MHz, δ(ppm): 141.76, 135.88, 128.60, 126.20, 107.38, 89.39, 84.74, 51.46. MS *m/z* (%) 158 (55), 140 (50), 129 (100), 115 (52), 102 (12), 77 (15), 51 (12).