

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of (Z)-organylthioenynes using KF/Al₂O₃/solvent as recyclable system

Diego Alves^a, Maraisa Sachini^a, Raquel G. Jacob^a, Eder J. Lenardão^a, Maria E. Contreira^a,
Lucielli Savegnago^b, Gelson Perin^{a,*}

^aInstituto de Química e Geociências, LASOL, Universidade Federal de Pelotas, UFPel, 96010-900, Pelotas-RS, Brazil

^bCentro de Desenvolvimento Tecnológico, CDTec, Universidade Federal de Pelotas, UFPel, 96010-900 Pelotas-RS, Brazil

ARTICLE INFO

Article history:

Received 14 September 2010

Revised 29 October 2010

Accepted 1 November 2010

Available online 5 November 2010

Keywords:

PEG-400

Glycerol

Thioenynes

ABSTRACT

PEG-400 and glycerol were successfully used as recyclable solvents for the synthesis of several organylthioenynes in good to excellent yields and high selectivity using solid supported catalyst (KF/Al₂O₃). This easy, general and improved method furnishes the corresponding alkenyl sulfides preferentially with Z configuration. The catalytic system and the glycerol or PEG-400 can be reused up to three times without previous treatment with comparable activity.

© 2010 Elsevier Ltd. Open access under the [Elsevier OA license](http://www.elsevier.com/locate/elsevier).

Vinyl sulfides are a valuable tool in organic reactions, acting as key intermediate in organic synthesis.¹ Besides, vinyl sulfides are present in natural occurring compounds such as griseoviridin, a type A streptogramin antibiotic, firstly isolated from *Streptomyces graminofaciens*² and benzylthiocredillidone, a yellow pigment isolated from the brightly red colored sponge *Crella spinulata*.³ The most common methods for the preparation of vinyl sulfides involve the addition of thiol, or thiolate anions, to alkynes.^{4–6} A drawback of most of these protocols is the use of toxic organic solvents, transition-metals catalysts⁴ or stoichiometric amounts of base.⁵ More recently, some improvements on selective preparation of vinyl sulfides have been described under solvent-free or catalyst-free conditions.^{6–8} Among the vinyl sulfides, organylthioenynes are very useful synthons in organic synthesis, because they can be used as precursor to enediynes and other functionalized olefins. However, the number of methodologies for accessing thioenynes is limited and the development of protocols for rigorous regio- and stereochemical controlled synthesis of these compounds remains yet a challenge.^{5b,6,9}

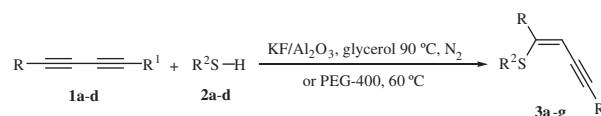
The use of potassium fluoride supported on alumina (KF/Al₂O₃) as a green catalytic system for a number of transformations has been increased.¹⁰ By using KF/Al₂O₃, the products can be easily isolated by filtration and the generation of large amounts of salts at the end of the synthesis, as well as the use of stoichiometric strong bases, can be avoided. On the other hand, the development of environmentally benign and clean synthetic methods, including those involving solvent-free or the use of alternative solvents, such as water, ionic liquids (ILs), and polyethylene glycol (PEG), has

increased in the last few years.¹¹ Despite several advantages, the solvent-free methods are restricted to systems where at least one of the reagents is a liquid at room temperature, while the use of ILs has some drawbacks, such as the high cost and the liberation of hazardous HF during recycling. In this line, the use of PEG and glycerol as promising media for organic reactions was recently demonstrated by us^{12,13} and others.^{14–18}

Recently, we have described several efficient approaches using KF/Al₂O₃.¹⁹ As a continuation of our studies we report herein the results of the hydrothiolation of 1,4-diorganyl-1,3-butadiynes **1** using KF/Al₂O₃ and PEG-400 or glycerol as recyclable solvents for this reaction (Scheme 1).^{20,21}

Initially, we chose 1,4-diphenyl-1,3-butadiyne **1a** and benzenethiol **2a** as standard starting materials in the presence of 3.0 mL of PEG-400. We examined the temperature, amount of KF/Al₂O₃ (50%) and the use of N₂ atmosphere. It was found that stirring a mixture of **1a** (1.0 mmol) and **2a** (1.0 mmol) in the presence of 0.07 g of KF/Al₂O₃ (50%) at room temperature, a mixture of (Z)- and (E)-1,4-diphenyl-2-(phenylthio)but-1-en-3-ynes **3a** was obtained in an overall yield of 34% after 26 h, together with a great amount of diphenyl disulfide (Table 1, entry 1).

Best results were obtained using 0.14 g and 0.28 g of KF/Al₂O₃, but long reaction times were required (Table 1, entries 2 and 3). On the other hand, when the same protocol was performed using 0.07 g of KF/Al₂O₃ on gentle heating (60 °C) the product was



Scheme 1.

* Corresponding author. Tel./fax: +55 5332757354.

E-mail address: perin@pq.cnpq.br (G. Perin).

Table 1
Optimization of the synthesis of thiobut-1-en-3-yne **3a**^{a,b}

Entry	Solvent	KF/Al ₂ O ₃ (g)	Temp. (°C)	Time (h)	Yield (%)
1	PEG-400	0.07	rt	26	34
2	PEG-400	0.14	rt	26	52
3	PEG-400	0.28	rt	26	87
4	PEG-400	0.07	60	1.5	93
5	PEG-400	0.06	60	7	85
6	PEG-400	0.04	60	8	74
7	PEG-400	None	60	2	13
8	Glycerol	0.07	60	6	8
9	Glycerol	0.07	90	6	64
10	Glycerol	0.07	120	6	45

^a Reaction conditions: Diyne **1a** (1.0 mmol); benzenethiol **2a** (1.0 mmol).

^b For all the tested examples, a little amount of (*E*)-**3a** was also formed.

obtained in 93% yield after only 1.5 h (*Z*:*E* ratio = 92:8, Table 1, entry 4). When smaller amounts of the catalyst were used, the product **3a** was obtained in lower yields (entries 5 and 6). In the absence of the catalytic system, **3a** was obtained only in 13% yield and with a loss of selectivity (*Z*:*E* ratio = 75:25, Table 1, entry 7).

Table 2
Hydrothiolation of butadiynes using KF/Al₂O₃ and glycerol or PEG as solvent

Entry	Butadiyne 1	Thiol 2	Product 3	Time (h)	Solvent	Ratio ^a (<i>Z</i>):(<i>E</i>)	Yield ^b (%)
1		C ₆ H ₅ SH 2a		1.5	PEG	92:8 (89:11) ^c (90:10) ^d	93 (89) ^e (92) ^d
2	1a	2a	(<i>Z</i>)- 3a + (<i>E</i>)- 3a	1.5	Glycerol ^e	95:5	64
3		<i>p</i> -ClC ₆ H ₄ SH 2b		2	PEG	89:11	86
4	1a	2b	(<i>Z</i>)- 3b + (<i>E</i>)- 3b	2	Glycerol ^e	88:12	79
5		^s C ₄ H ₉ SH 2c		1	PEG	95:5	95
6	1a	2c	(<i>Z</i>)- 3c + (<i>E</i>)- 3c	2.5	Glycerol ^e	93:7	39
7		<i>p</i> -CH ₃ OC ₆ H ₄ SH 2d		2.5	PEG	100:0	78
8	1a	2d	(<i>Z</i>)- 3d + (<i>E</i>)- 3d	3	Glycerol ^e	100:0	62
9		C ₆ H ₅ SH 2a		2	PEG	100:0	83
10	1b	2a	(<i>Z</i>)- 3e + (<i>E</i>)- 3e	1.5	Glycerol ^e	100:0	88
11		C ₆ H ₅ SH 2a		2	PEG	100:0	97
12	1c	2a	(<i>Z</i>)- 3f + (<i>E</i>)- 3f	2	Glycerol ^e	100:0	98
13		C ₆ H ₅ SH 2a		2	PEG	100:0	92

^a Determined by GC and ¹H NMR of the crude reaction mixture and confirmed after isolation of pure products.

^b Yields of pure products isolated by column chromatography (hexanes/AcOEt) and identified by mass spectrometry, ¹H and ¹³C NMR.^{5b,9}

^c Reaction performed in a 5 mmol scale.

^d Reaction was performed in the presence of the hydroquinone.

^e Reaction was performed under N₂ atmosphere.

Besides, the use of glycerol as a solvent was evaluated. However, when the reactions were performed in the presence of glycerol at the same temperature (60 °C), **3a** was formed in poor yield (Table 1, entry 8). To our satisfaction, by increasing the temperature to 90 °C the reaction proceeds smoothly, furnishing the product **3a** in satisfactory yield (*Z*:*E* ratio = 95:5, Table 1, entry 9). When the temperature was increased to 120 °C, poor yields were obtained (Table 1, entry 10). In an optimized reaction, 1,4-diphenyl-1,3-butadiyne **1a** (1.0 mmol) was dissolved in glycerol (3 mL) and reacted with benzenethiol **2a** (1.0 equiv) at 90 °C during 6 h under N₂ atmosphere, yielding **3a** in 64% yield (Scheme 1).

Using the optimized conditions,²¹ the protocol was extended to other thiols and symmetric conjugated butadiynes to produce organothioenynes **3b–f** in good to excellent yields (Table 2). The small yield observed when glycerol was used can be attributed to a competition between the hydrothiolation reaction and the thiol oxidation to afford the respective disulfides. For all the studied examples, a variable amount of disulfide was isolated. This is in agreement with a recent report of our group describing the clean oxidation of thiols to disulfide in the presence of KF/Al₂O₃.^{19b}

Satisfactory results were achieved using alkyl thiols and aryl thiols containing electron donating or electron withdrawing groups (Table 2, entries 1–8). The use of diynols afforded good to excellent yields of desired products (Table 2, entries 9–12). Additionally, when the unsymmetrical 2-methyl-6-phenylhexa-3,5-diyne-2-ol **1d** reacted with benzenethiol **2a**, we observed exclusively the formation of (*Z*)-2-methyl-6-phenyl-3-(phenylthio)hex-3-en-5-yn-2-ol **3g** in 92% yield (Table 2, entry 13). In this case, the propargylic triple bond underwent addition of the phenylthiolate anion preferentially than the triple bond containing the phenyl group.^{5b} A reuse study of the solvent/catalytic system was carried out for the reaction.²² After completion of hydrothiolation, the reaction mixture was diluted with hexane/ethyl acetate (90:10) and the product was isolated. The remaining PEG or glycerol/KF/Al₂O₃ mixture was directly reused for further reactions. It was observed that a good level of efficiency was maintained even after three cycles. Thus, the product **3a** was obtained in 93%, 89%, 80% yields using PEG as solvent, while using glycerol, the isolated yields were 64%, 55%, and 48% after successive cycles.

Concerning the stereochemistry of products, the formation of (*Z*)-enyne was preferential for all the tested examples. Thus, *Z*-**3a** was obtained preferentially from the reaction of 1,4-diorganyl-1,3-butadiyne **1a** with benzenethiol **2a** (*Z*:*E* ratio = 92:8, Table 2, entry 1), while 4-methoxybenzenethiol **2d** afforded exclusively the respective (*Z*)-adduct **3d** (entries 7 and 8). A similar 100% stereoselectivity was observed when the diynols **1b** and **1c** were used, giving exclusively the respective adducts **3e** and **3f** with *Z* configuration (Table 2, entries 9–12). Comparable result was obtained using a radical inhibitor. Thus, the reaction of **1a** with **2a** was performed in the presence of the hydroquinone affording the product **3a** in 92% yield and with a *Z*:*E* ratio = 90:10 (Table 2, entry 1). This result is in according with a probable anionic mechanism.

In summary, an efficient and clean protocol was developed for the selective synthesis of thiobutenynes. The reaction is promoted by KF/Al₂O₃ and can be performed using glycerol or PEG as solvents. The reactions proceeds easily and the products were obtained in good to excellent yields. The use of glycerol as a renewable, non-toxic, and recyclable solvent opens new possibilities for future applications of glycerol in green and sustainable chemistry.

Acknowledgments

We are grateful to FINEP, CAPES, CNPq, and FAPERGS/PRONEX (10/0005-1 and 10/0130-3) for the financial support.

References and notes

- For the synthetic utility of vinyl sulfides, see, for example: (a) Aucagne, V.; Lorin, C.; Tatibouët, A.; Rollin, P. *Tetrahedron Lett.* **2005**, *46*, 4349; (b) Muraoka, N.; Mineno, M.; Itami, K.; Yoshida, J.-I. *J. Org. Chem.* **2005**, *70*, 6933; (c) Woodland, C. A.; Crawley, G. C.; Hartley, R. C. *Tetrahedron Lett.* **2004**, *45*, 1227; (d) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239; (e) Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*; CRC Press: Boca Raton, FL, 1991; Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; Wiley & Sons: New York, 1996.
- (a) Marcantoni, E.; Massaccesi, M.; Petrini, M. *J. Org. Chem.* **2000**, *65*, 4553; (b) Kuligowski, C.; Bezzenine-Lafollée, S.; Chaume, G.; Mahuteau, J.; Barrière, J.-C.; Bacqué, E.; Pancrazi, A.; Ardisson, J. *J. Org. Chem.* **2002**, *67*, 4565.
- Lan, H. W.; Cooke, P. A.; Pattenden, G.; Bandaranayake, W. M.; Wickramasinghe, W. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 847.
- Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205; Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614; (b) Weiss, C. J.; Wobser, S. D.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 2062; (c) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108; (d) Malyshev, D. A.; Scott, N. M.; Marion, N.; Stevens, E. D.; Ananikov, V. P.; Beletskaya, I. P.; Nolan, S. P. *Organometallics* **2006**, *25*, 4462.
- (a) Waters, M. S.; Cowen, J. A.; McWilliams, J. C.; Maligres, P. E.; Askin, D. *Tetrahedron Lett.* **2000**, *41*, 141; (b) Dabdoub, M. J.; Dabdoub, V. B.; Lenardão, E. J.; Hurtado, G. R.; Barbosa, S. L.; Guerrero, P. G., Jr.; Nazário, C. E. D.; Viana, L. H.; Santana, A. S.; Baroni, A. C. M. *Synlett* **2009**, 986; (c) Wadsworth, D. H.; Detty, M. R. *J. Org. Chem.* **1980**, *45*, 4611.
- Manarin, F.; Roehrs, J. A.; Prigol, M.; Alves, D.; Nogueira, C. W.; Zeni, G. *Tetrahedron Lett.* **2007**, *48*, 4805.
- (a) Ananikov, V. P.; Orlov, N. V.; Beletskaya, I. P. *Organometallics* **2006**, *25*, 1970; (b) Corma, A.; González-Arellano, C.; Iglesias, M.; Sánchez, F. *Appl. Catal. A: Gen.* **2010**, *375*, 49; (c) Banerjee, S.; Das, J.; Santra, S. *Tetrahedron Lett.* **2009**, *50*, 124; (d) Sridhar, R.; Surendra, K.; Krishnaveni, N. S.; Srinivas, B.; Rao, K. R. *Synlett* **2006**, 3495.
- Schneider, C. C.; Godoi, B.; Prigol, M.; Nogueira, C. W.; Zeni, G. *Organometallics* **2007**, *26*, 4252.
- (a) Volkov, A. N.; Volkova, K. A.; Levanova, E. P.; Trofimov, B. A. *Zh. Org. Khim.* **1982**, *18*, 2049; (b) Volkov, A. N.; Volkova, K. A. *Russ. J. Org. Chem.* **2004**, *40*, 1679; (c) Zeni, G.; Nogueira, C. W.; Pena, J. M.; Pilissão, C.; Menezes, P. H.; Braga, A. L.; Rocha, J. B. T. *Synlett* **2003**, 579; (d) Zeni, G.; Stracke, M. P.; Lissner, E.; Braga, A. L. *Synlett* **2003**, 1880.
- (a) Basu, B.; Das, P.; Das, S. *Curr. Org. Chem.* **2008**, *12*, 141; (b) Blass, B. E. *Tetrahedron* **2002**, *58*, 9301.
- See, for instance: (a) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015; (b) Dupont, J.; Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667; (c) Dupont, J.; Consorti, C. S.; Spencer, J. J. *Braz. Chem. Soc.* **2000**, *11*, 337; (d) Consorti, C. S.; Souza, R. F.; Dupont, J.; Suarez, P. A. Z. *Quím. Nova* **2001**, *24*, 830; Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: New York, 2002; (f) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (g) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772; (h) Davis, J. H., Jr.; Fox, P. A. *Chem. Commun.* **2003**, 1209.
- Silveira, C. C.; Mendes, S. R.; Líbero, F. M.; Lenardão, E. J.; Perin, G. *Tetrahedron Lett.* **2009**, *50*, 6060.
- (a) Lenardão, E. J.; Trecha, D. O.; Ferreira, P. C.; Jacob, R. G.; Perin, G. *J. Braz. Chem. Soc.* **2009**, *20*, 93; (b) Lenardão, E. J.; Silva, M. S.; Sachini, M.; Lara, R. G.; Jacob, R. G.; Perin, G. *ARKIVOC* **2009**, xi, 221; (c) Perin, G.; Mello, L. G.; Radatz, C. S.; Savegnago, L.; Alves, D.; Jacob, R. G.; Lenardão, E. J. *Tetrahedron Lett.* **2010**, *51*, 4354.
- (a) Gu, Y.; Jérôme, F. *Green Chem.* **2010**, *12*, 1127; (b) Wolfson, A.; Dlugy, C. *Chem. Pap.* **2007**, *61*, 228.
- Wolfson, A.; Litvak, G.; Dlugy, C.; Shotland, Y.; Tavor, D. *Ind. Crops Prod.* **2009**, *30*, 78.
- Wolfson, A.; Dlugy, C.; Shotland, Y. *Environ. Chem. Lett.* **2007**, *5*, 67.
- Wolfson, A.; Dlugy, C.; Shotland, Y.; Tavor, D. *Tetrahedron Lett.* **2009**, *50*, 5951.
- (a) He, F.; Li, P.; Gu, Y.; Li, G. *Green Chem.* **2009**, *11*, 1767; (b) Karam, A.; Villandier, N.; Delamplé, M.; Koerkamp, C. K.; Douliez, J.-P.; Granet, R.; Krausz, P.; Barrault, J.; Jérôme, F. *Chem. Eur. J.* **2008**, *14*, 10196; (c) Gu, Y.; Barrault, J.; Jérôme, F. *Adv. Synth. Catal.* **2008**, *350*, 2007.
- (a) Lenardão, E. J.; Ferreira, P. C.; Jacob, R. G.; Perin, G.; Leite, F. P. L. *Tetrahedron Lett.* **2007**, *48*, 6763; (b) Lenardão, E. J.; Lara, R. G.; Silva, M. S.; Jacob, R. G.; Perin, G. *Tetrahedron Lett.* **2007**, *48*, 7668; (c) Perin, G.; Jacob, R. G.; Botteselle, G. V.; Kublik, E. L.; Lenardão, E. J.; Cella, R.; Santos, P. C. S. *J. Braz. Chem. Soc.* **2005**, *16*, 857; (d) Silva, M. S.; Lara, R. G.; Marczewski, J. M.; Jacob, R. G.; Lenardão, E. J.; Perin, G. *Tetrahedron Lett.* **2008**, *49*, 1927; (e) Victoria, F. N.; Radatz, C. S.; Sachini, M.; Jacob, R. G.; Perin, G.; da Silva, W. P.; Lenardão, E. J. *Tetrahedron Lett.* **2009**, *50*, 6761.
- Preparation of alumina supported potassium fluoride:²³ Alumina (4.0 g of Al₂O₃ 90, 0.063–0.200 mm, Merck), KF·2H₂O (6.0 g) and water (10 mL) were mixed in a 50 mL beaker and the suspension stirred at 65 °C for 1 h. The resulting solid was dried at 80 °C for 1 h and subsequently 4 h at 300 °C in an oven and finally cooled to room temperature in a desiccator. The content of KF is about 50% (m/m).
- General procedure for the synthesis of thiobutenynes 3*: To a mixture of 1,4-diphenyl-1,3-butadiyne (**1a**; 0.202 g; 1 mmol), benzenethiol (**2a**; 0.110 g; 1 mmol) and PEG or glycerol (3 mL), KF/Al₂O₃ (0.07 g, obtained as described above) was added at room temperature. The reaction mixture was allowed to stir at 60 °C for the time indicated in Table 2. After that, the reaction mixture was washed with a mixture of hexane/ethyl acetate (90:10; 3 × 5 mL) and the upper organic phase was separated from the PEG or glycerol containing the supported catalyst, dried with MgSO₄ and evaporated under reduced pressure. The product was isolated by column chromatography using hexane as eluent, yielding a mixture of *Z*-**3a** and *E*-**3a** (0.290 g, 93%, *Z*:*E* ratio = 92:8). ¹H NMR (200 MHz, CDCl₃) δ (*Z* + *E*) 7.43–7.55 (m, 4H); 7.05–7.33 (m, 11H); (*Z* isomer) 6.33 (s, 1H); (*E* isomer) 5.30 (s, 1H). MS *m/z* (rel. int.%) 312 (M⁺, 100.0), 202 (99.7), 121 (50.0), 77 (19.5).
- Reuse*: To a round-bottomed flask containing 1,4-diphenyl-1,3-butadiyne **1a** (1.0 mmol), benzenethiol **2a** (1.0 mmol) and solvent (3 mL) was added Al₂O₃/KF. The reaction mixture was allowed to stir at 60 °C (using PEG-400) or at 90 °C (using glycerol) for 1.5 h. After that, the reaction mixture was washed with a mixture of hexane/ethyl acetate (90:10; 3 × 5 mL) and the upper organic phase was separated from solvent/KF/Al₂O₃. The product was isolated according procedure above. The mixture solvent/KF/Al₂O₃ was dried under vacuum and reused for further reactions.
- Wang, S.-X.; Li, J.-T.; Yang, W.-Z.; Li, T.-S. *Ultrason. Sonochem.* **2002**, *9*, 159.