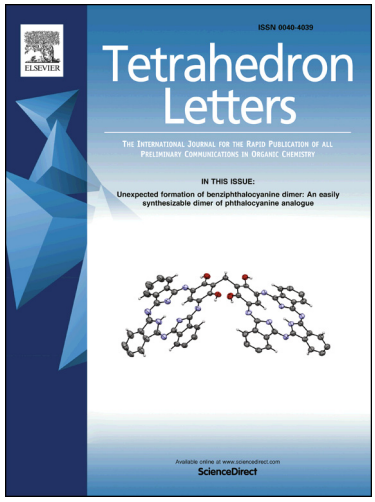


Lewis acid promoted reaction of tetraalkynylstannanes with acyl chlorides: an effective approach towards alkynyl ketones

Andrey S. Levashov, Dmitrii S. Buryi

PII: S0040-4039(17)31315-1
DOI: https://doi.org/10.1016/j.tetlet.2017.10.035
Reference: TETL 49397

To appear in: *Tetrahedron Letters*

Received Date: 14 August 2017
Revised Date: 5 October 2017
Accepted Date: 14 October 2017

Please cite this article as: Levashov, A.S., Buryi, D.S., Lewis acid promoted reaction of tetraalkynylstannanes with acyl chlorides: an effective approach towards alkynyl ketones, *Tetrahedron Letters* (2017), doi: https://doi.org/10.1016/j.tetlet.2017.10.035

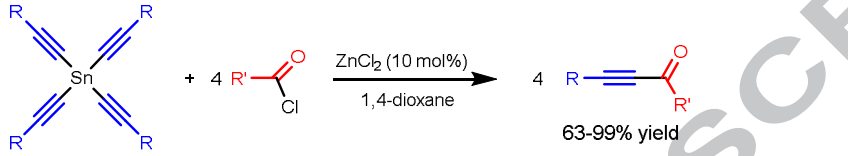
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Lewis acid promoted reaction of tetraalkynylstannanes with acyl chlorides: an effective approach towards alkynyl ketones

Leave this area blank for abstract info.

Andrey S. Levashov* and Dmitrii S. Buryi



R = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, *n*-Bu R' = Ph, 4-*t*-BuC$_6$H$_4$, 3-MeOC$_6$H$_4$, Me, *n*-Pr, *i*-Pr, CH$_3$(CH$_2$)$_{14}$

Tetrahedron Letters
journal homepage: www.elsevier.com

Lewis acid promoted reaction of tetraalkynylstannanes with acyl chlorides: an effective approach towards alkynyl ketones

Andrey S. Levashov[a] *and Dmitrii S. Buryi [a]

[a]*Department of Organic Chemistry & Technologies, Kuban State University, 149 Stavropolskaya str., 350040 Krasnodar, Russian Federation*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

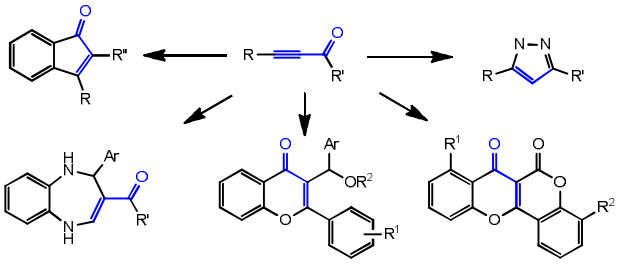
Keywords:
alkynylstannanes
acyl chlorides
Lewis acid
alkynyl ketones

ABSTRACT

Tetraalkynylstannanes were found to be atom-economical nucleophilic reagents for the synthesis of α,β-acetylenic ketones. The scope and some limitations of the method are discussed.

α,β-Acetylenic ketones are widely used in organic synthesisas starting reagents for the preparation of indenones,[1,2] benzodiazepines,[3] chromones,[4,5] frutinones,[6] pyrazoles,[7] and phosphonylated indenones[8] (Scheme 1).

α,β-Acetylenic ketones can be prepared by the Sonogashira coupling of terminal acetylenes and acyl halides; however, this reaction requires an expensive palladium catalyst,[9-11] or sophisticated mesoporous silicates.[12] To date, the most frequently used approaches for the synthesis of acetylenic ketones are based on the reaction of metal acetylides with acyl chlorides. It should be noted that the nature of the organometallic reagent strongly affects the reaction conditions and the yields of the target ketones, as well as by-product formation (for details, see review[13]). Another important factor worth considering is the so-called *E*-factor, which is defined as the mass ratio of waste to desired product.[14] From this point of view, lithium, sodium, and potassium acetylides are among the most attractive organometallic reagents for the synthesis of functionalized acetylenes. However, due to their high reactivity with acyl halides, this reaction is difficult to control and cannot be stopped precisely at the stage of alkynyl ketone formation. Special interest has been given to trialkyltin acetylides (Alk_3Sn-C≡C-R), since these mild reagents are tolerant towards a number of functional groups and react smoothly in the presence of Pd catalysts to give functionalized acetylenes in high yields.[15-21] No catalyst is required when more active acyl iodides are used.[22] However, the high molecular weight, and hence the high *E*-factor of the trialkyltin species, make the use of these acetylides unattractive for both laboratory and large-scale synthesis.



Scheme 1. Selected reactions of alkynyl ketones

Another problem with the use of trialkyltin reagents is the high toxicity. Nevertheless, despite these drawbacks, organostannanes are utilised as effective and atom economical reagents for various alkynylation reactions.

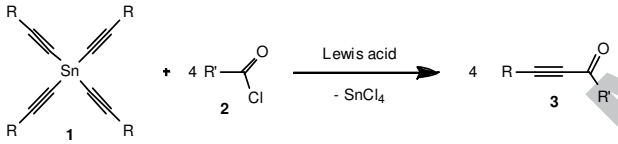
The solution came with the replacement of monoalkynylstannanes with tetraalkynyltin reagents $(R\text{-}C{\equiv}C)_4Sn$. The advantages of tetraalkynylstannanes are low toxicity (since Sn–C(sp) bonds tend to readily hydrolyze even with atmospheric moisture to give only the corresponding inorganic tin species) and the low molecular weight of the tin residue. Thus, in contrast to trialkyltin reagents (e.g. frequently used tributyltin derivatives bearing the Bu_3Sn residue with a molecular weight of 290), tetraalkynyltin reagents are more effective, discarding only tin atoms as waste (the molecular weight is about 30 Da per acetylide unit), and hence could be compared with alkali metal acetylides in terms of atom economy. It should be noted that alkynyltin trichlorides could also be used as a less toxic alternative to trialkyltin reagents. However, alkynyltin

* Corresponding author. e-mail: aslevashov@mail.ru, phone/fax: +78612199570

trichlorides cannot be considered as atom-economical reagents, and react with acyl chlorides to give acetylenic ketones in only moderate yields (21-63%).[23]

It is noteworthy that for tetraorganyltin compounds, only a few reactions are known to involve all four substituents at the tin atom. Thus, the reactions of tetraallylstannanes with imines,[24] aldehydes or ketones,[25–27] as well as other electrophiles[26] have been described. Recently, we reported the Stille-type coupling reaction of tetraalkynylstannanes with aryl halides leading to aryl acetylenes and $SnHal_4$,[28] and aldehydes leading to alkynyl ketones.[29,30] It was briefly mentioned by Neumann and Kleiner[31] that the reaction of a tetraalkynylstannane with acetyl chloride gave an acetylenic ketone in only 50% yield. In our opinion, the reaction scope of tetraalkynylstannanes as nucleophilic agents remains limited, despite tetraalkynyltin reagents being easily available by the direct alkynylation of either $SnCl_4$[32] or tin tetra(*N*,*N*-diethylcarbamate).[33]

Herein, we report an effective and time-saving protocol for the synthesis of acetylenic ketones *via* the reaction of tetraalkynylstannanes **1** with acyl chlorides **2**. This reaction starts easily in the presence of Lewis acid catalysts and is autocatalytic (Scheme 2). The presence of tin tetrachloride, which is formed in the reaction, accelerates the acylation process but also leads to some resinification of the acetylenic ketone **3**. The nature of the solvent also exerts a significant influence – thus, the use of 1,4-dioxane, which forms a complex with tin tetrachloride,[34] leads to lower acidity and decreases side-reactions to some extent.



Scheme 2. Reaction of tetraalkynylstannanes **1** with acyl chlorides **2**.

The effects of solvent and catalyst loading on the yield of acetylenic ketone **3aa** in the model reaction of stannane **1a** with benzoyl chloride **2a** is shown in the Table 1. The use of increased catalyst loading accelerates the reaction but also lowers the yield due to by-product formation. Tetraalkynylstannane **1a** did not react with benzoyl chloride below 80 °C. Meanwhile, the yield of ketone **3aa** tended to decrease with further temperature increases. The use of $ZnCl_2$ as a catalyst was found to be optimal, giving the highest product yields. The reaction did not proceed in the presence of basic catalysts. Another important factor that influences the reaction process is the reactant concentration. Thus, when the concentration of benzoyl chloride **2a** was doubled (increased from 1.39 mmol/mL to 2.78 mmol/mL), the yield of the target ketone **3aa** increased significantly, despite the reaction mixture becoming thick as the reaction reached completion due to the formation of a complex between $SnCl_4$ and 1,4-dioxane. The formation of a thick slurry was taken to indicate that the reaction had proceeded to completion.

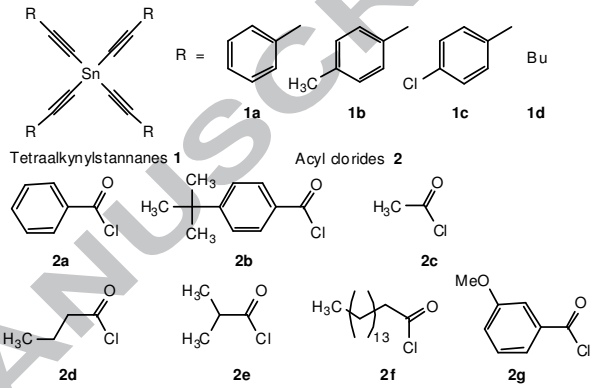


Figure 1. Scope of stannanes **1** and acyl chlorides **2**

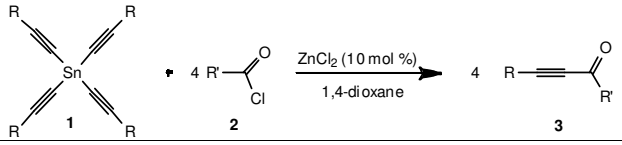
The various tetraalkynylstannanes **1** and acyl chlorides **2** explored for this reaction are shown in Figure 1. In order to avoid hydrolysis, all of the reactions were conducted in dry solvents under an argon atmosphere. The preparative yields of the alkynyl ketones **3** are shown in Table 2. Lipophillic acid chlorides were noticeably more active in this reaction than aromatic acid chlorides. Thus, the reaction of tetraalkynylstannane **1a** with acetyl chloride **2c** was complete within 30 min even at 40 °C, affording acetylenic ketone **3ac** in 99% isolated yield.

Table 1. Effect of solvent, catalyst and reaction time on the model reaction of tetraalkynylstannane **1a** with benzoyl chloride **2a**[a]

Solvent	Catalyst (mol%)	T (°C)	Time (h)	Yield **3aa** (%)[c]
THF	-	66	6	no reaction
PhMe	-	100	10	32
DCE	-	80	5	64
DCE	$ZnCl_2$ (10)	80	1	60
1,4-dioxane	-	80	5	4
1,4-dioxane	-	100	5	66
1,4-dioxane	$ZnCl_2$ (10)	100	1.5	66
1,4-dioxane	$ZnCl_2$ (10)	80	3	79
1,4-dioxane	$ZnCl_2$ (10)	80	3	98[b]
1,4-dioxane	$ZnCl_2$ (10)	60	3.5	no reaction
1,4-dioxane	$ZnCl_2$ (50)	80	3.5	63
1,4-dioxane	$ZnCl_2$ (100)	80	2	57
1,4-dioxane	$ZnBr_2$ (10)	80	3.5	64
1,4-dioxane	$Zn(CF_3SO_3)_2$ (10)	80	1	61
1,4-dioxane	Et_3N (100)	100	4	no reaction
1,4-dioxane	Pyridine (100)	80	2	no reaction

[a]Reagents and conditions: $(Ph\text{-}C{\equiv}C)_4Sn$ **1a** (0.55 mmol), benzoyl chloride **2a** (2.0 mmol), catalyst, solvent (1.44 mL); [b]1,4-dioxane (0.72 mL). [c]Yields determined by GC-MS by the ratio of starting material to product.

Table 2. Examination of the reaction scope.[a]



Alkynyl ketones **3**	R	R'	T (°C)	Time (min)	Yield (%)[b]
3aa	Ph	Ph	80	150	67
3ab	Ph	4-*t*-BuC_6H_4	80	75	80
3ag	Ph	3-MeOC_6H_4	80	100	66
3bb	4-MeC_6H_4	4-*t*-BuC_6H_4	80	60	63
3ac	Ph	Me	40	30	99
3ad	Ph	Pr	60	10	81
3ae	Ph	*i*-Pr	60	20	78
3af	Ph	$CH_3(CH_2)_{14}$	60	30	95
3bc	4-MeC_6H_4	Me	40	20	87
3dc	Bu	Me	40	30	74
3bd	4-MeC_6H_4	Pr	60	10	88
3ce	4-ClC_6H_4	*i*-Pr	60	10	85
3cf	4-ClC_6H_4	$CH_3(CH_2)_{14}$	60	30	89

[a]Reagents and conditions: $(RC{\equiv}C)_4Sn$ **1a** (0.55 mmol), R'C(O)Cl **2a** (2.0 mmol), $ZnCl_2$ (0.2 mmol), 1,4-dioxane (0.72 mL). [b]Isolated yield.

The reaction of stannanes **1** with other lipophillic acid chlorides required heating at 60 °C; the reaction was complete within 10-30 minutes, furnishing acetylenic ketones **3a-x** in good yields (78-95%). It should be noted that long-chain lipophillic acid chlorides also reacted well to give the corresponding long-chain ketones in high yields (see Table 2 and ESI, Table 1).

In summary, we have proposed a new, fast and atom-economical method for the preparation of α-acetylenic ketones, starting from mild nucleophilic reagents – tetraalkynylstannanes. The method is suitable for the synthesis of long-chain acetylenic ketones.

Acknowledgments

The publication was financially supported by the Russian Ministry of Education and Science (grants of the President of the Russian Federation СП-2272.2016.1). This work was performed with the use of equipment of the Research and Educational Centrum "Diagnostics of the structure and properties of nanomaterials."

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://

References and notes

1 Y.-K. Song, P.-C. Qian, F. Chen, C.-L. Deng and X.-G. Zhang, *Tetrahedron*, **2016**, 72, 7589–7593.
2 A. V. Vasilyev, S. Walspurger, P. Pale and J. Sommer, *Tetrahedron Lett.*, **2004**, 45, 3379–3381.
3 L. Yin and L. Wang, *Tetrahedron Lett.*, **2016**, 57, 5935–5940.
4 M. Jonušis, L. Šteinys, R. Bukšnaitienė and I. Čikotienė, *Synthesis.*, **2016**, 48, A-1.
5 B. Schmidt, M. Riemer and U. Schilde, *European J. Org. Chem.*, **2015**, 7602–7611.
6 M. Yoshida, K. Saito, Y. Fujino and T. Doi, *Tetrahedron*, **2014**, 70, 3452–3458.
7 R. Harigae, K. Moriyama and H. Togo, *J. Org. Chem.*, **2014**, 79, 2049–2058.
8 J. Zhou, G. L. Zhang, J. P. Zou and W. Zhang, *European J. Org. Chem.*, **2011**, 3412–3415.
9 D. A. Alonso, C. Nrajera, M. C. Pacheco, *J. Org. Chem.*, **2004**, 69, 1615-1619.
10 S. Santra, K. Dhara, P. Ranjan, P. Bera, J. Dash, S. K. Mandal, *Green Chem.*, **2011**, 13, 3238–3247.
11 S. Hossain, Ji-hoon Park, Min-kyu Park, Myung-Jong Jin, *J. Korean Chem. Soc.*, **2013**, 57, 411-415.
12 K. R. Reddy, M. Suresh, M. L. Kantam, S. K. Bhargava, P. Srinivasu, *Ind. Eng. Chem. Res.*, **2014**, *53* (49), 18630–18636.
13 R. K. Dieter, *Tetrahedron*, **1999**, 55, 4177–4236.
14 R. A. Sheldon, *Green Chem.*, **2007**, 9, 1273–1283.
15 R. Lerebours, A. Camacho-soto and C. Wolf, *J. Org. Chem.*, **2005**, 70, 8601–8604.
16 M. Shu, J. L. Loebach, K. A. Parker, S. G. Mills, K. T. Chapman, D. M. Shen, L. Malkowitz, M. S. Springer, S. L. Gould, J. A. DeMartino, S. J. Siciliano, K. Lyons, J. V. Pivnichny, G. Y. Kwei, A. Carella, G. Carver, K. Holmes, W. a. Schleif, R. Danzeisen, D. Hazuda, J. Kessler, J. Lineberger, M. D. Miller and E. A. Emini, *Bioorganic Med. Chem. Lett.*, **2004**, 14, 947–952.
17 J. M. Yeung, R. D. Mortimer and P. G. Collins, *J. Agric. Food Chem.*, **1996**, 44, 376–380.
18 A. S. Golubev, N. Sewald and K. Burger, *Tetrahedron*, **1996**, 52, 14757–14776.
19 P. Mazur and K. Nakanishi, *J. Org. Chem.*, **1992**, 57, 1047–1051.
20 J. W. Labadie, D. Tueting and J. K. Stille, *J. Org. Chem.*, **1983**, 48, 4634–4642.
21 M. W. Logue and K. Teng, *J. Org. Chem.*, **1982**, 47, 2549–2553.
22 M. G. Voronkov, A. A. Trukhina, N. N. Vlasova, R. G. Mirskov, O. G. Yarosh, *Russ. J. Org. Chem.,***2006**, 42, 23-26.
23 S. A. Shelkunov, O. A. Sivolobova, Z. M. Muldahmetov, *Russ. J. Gen. Chem*, **2000**, 70, 539-541.
24 X. N. Wei, L. Y. Liu, B. Wang, W. X. Chang and J. Li, *Chinese Chem. Lett.*, **2009**, 20, 40–43.
25 X. Zhang, R. Qiu, N. Tan, S. Yin, J. Xia, S. Luo and C. T. Au, *Tetrahedron Lett.*, **2010**, 51, 153–156.
26 W. J. Scott, A. F. Moretto. Tetraallylstannane. *e-EROS Encyclopedia of Reagents for Organic Synthesis*, Wiley, 2001.
27 A. Yanagisawa, H. Inoue, M. Morodome and H. Yamamoto, *J. Am. Chem. Soc.*, **1993**, **115**, 10356–10357.
28 A. S. Levashov, D. S. Buryi, O. V. Goncharova, V. V. Konshin, V. V. Dotsenko and A. A. Andreev, *New J. Chem.*, **2017**, 41, 2910–2918.
29 A. Levashov, N. A. Aksenov, I. V Aksenova and V. V Konshin,

New J. Chem., 2017, **41**, 8297 - 8304.

30 A. S. Levashov, D. S. Buryi, V. V. Konshin, V. V. Dotsenko, N. A. Aksenov and I. V. Aksenova, *Russ. J. Gen. Chem.*, **2017**, 87, 1627–1630.

31 W. P. Neumann and F. G. Kleiner, *Liebigs Ann. der Chemie*, **1968**, 716, 29–36.

32 A. S. Levashov, A. A. Andreev and V. V. Konshin, *Tetrahedron Lett.*, **2015**, 56, 1870–1872.

33 A. S. Levashov, A. A. Andreev, D. S. Buryi and V. V. Konshin, *Russ. Chem. Bull.*, **2014**, 63, 775–776.

34 S. Ichiba, M. Mishima, H. Sakai and H. Negita, *Bull. Chem. Soc. Jpn.*, **1968**, 41, 49–52.

35 **Typical procedure for the synthesis of alkynyl ketones 3**. A 2-mL sealable Wheaton vial was charged with anhydrous $ZnCl_2$ (27.3 mg, 0.2 mmol), 1,4-dioxane (0.72 mL), tetra(phenylethynyl)tin **1a** (287.8 mg, 0.55 mmol) and hexadecanoyl chloride **2f** (549.7 mg, 2.0 mmol). The reaction mixture was stirred at 60 °C for 30 min, then treated with 1M aqueous HCl (10 ml). The product was extracted with $CHCl_3$ (3×10 ml) and purified by column chromatography (eluent – hexane, then 1:1 hexane-toluene, then toluene) to give ketone **3af** in 95% yield (571.3 mg), as a light yellow solid. After recrystallization from heptane – colouress crystals, m.p. 41.4-41.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, CH_3), 1.21-1,37 (m, 24H, CH_2), 1.73 (quint, 2H, C^5H_2), 2.65 (t, 2H, C^4H_2), 7.35-7.39 (m, 2H, ArH), 7.42-7.46 (m, 1H, ArH), 7.55-7.57 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.08, 22.66, 24.17, 28.99, 29.33, 29.42, 29.57, 29.63, 29.65, 31.90, 45.54, 87.85, 90.48, 120.08, 128.57, 130.57, 132.99, 188.25.

Highlights

- An atom-economical method for the preparation of α,β-acetylenic ketones from tetraalkynylstannanes.
- The reaction starts in the presence of Lewis acid catalysts and is autocatalytic.
- The method is suitable for the synthesis of long-chain acetylenic ketones.