Novel Synthesis of Substituted Thiophenes by Palladium-Catalyzed Cycloisomerization of (*Z*)-2-En-4-yne-1-thiols
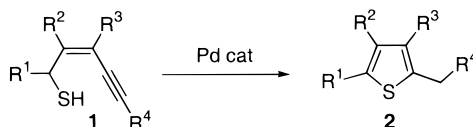
Bartolo Gabriele,* Giuseppe Salerno,*,† and Alessia Fazio

Dipartimento di Chimica, Università della Calabria, 87030 Arcavacata di Rende, Cosenza, Italy

b.gabriele@unical.it

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ABSTRACT

The first example of palladium-catalyzed cycloisomerization of (*Z*)-2-en-4-yne-1-thiols **1** to give substituted thiophenes **2** is reported. Cycloisomerization reactions are carried out under nitrogen at 25−100 °C in *N,N*-dimethylacetamide as the solvent in the presence of catalytic amounts of PdI$_2$ in conjunction with KI to give the corresponding thiophenes in 43−94% yield.

Thiophenes are a very important class of heterocyclic compounds. A variety of molecules containing the thiophene ring display a wide range of biological activity and find application as pharmaceuticals[1] or fragrance compounds.[2] Moreover, they are also useful synthetic intermediates: for example, in the preparation of new conducting polymers[3] or nonlinear optical materials.[4]

Substituted thiophenes can be prepared by proper functionalization of the thiophene ring, usually through α-metalation or β-halogenation.[1] However, annulation reactions of suitably substituted acyclic precursors represent an attractive alternative methodology, which may allow direct regioselective preparation of the target molecule. Recently, several new methods have been developed which illustrate the utility of the last approach.[5]

We report herein a novel synthesis of substituted thiophenes **2**, based on Pd-catalyzed cycloisomerization[6] of the readily available[7] (*Z*)-2-en-4-yne-1-thiols **1** (eq 1).[8]
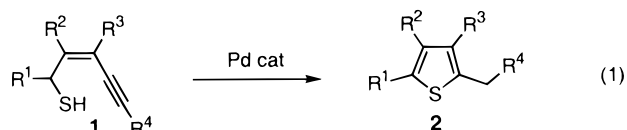

(1)

Table 1 reports the results obtained with different enyne-thiols **1**. Reactions were carried out at 25−100 °C in the

† E-mail: g.salerno@unical.it.

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Table 1. Synthesis of Thiophenes **2** by Pd-Catalyzed Cycloisomerization of (Z)-2-En-4-yne-1-thiols **1**[a]

entry	1	R¹	R²	R³	R⁴	time (h)	yield (%)[b]
1[c,d]	**1a**	H	H	Me	H	2	45 (36)
2[c]	**1b**	Et	H	Me	H	1	80 (71)
3	**1c**	Ph	H	Me	H	1.5	65 (58)
4	**1d**	H	H	Me	Bu	15	52 (44)
5	**1e**	H	H	Me	Ph	8	64 (56)
6[e]	**1f**	H	Et	H	Bu	1	94 (89)

[a] Unless otherwise noted, all reactions were carried out under nitrogen in anhydrous DMA (2 mmol of **1**/mL of DMA) at 100 °C using PdI₂:KI: substrate molar ratio 1:2:100. [b] GLC yields (isolated yields) based on **1**. [c] The reaction was carried out without solvent. [d] Substrate:PdI₂ molar ratio 50. [e] The reaction was carried out at 25 °C.

presence of PdI₂ (1−2%) in conjunction with 2 equiv of KI, the latter being necessary for solubilizing PdI₂ in the reaction medium. As we already observed in the Pd(II)-catalyzed cycloisomerization of (Z)-2-en-4-yn-1-ols leading to furans,[8a] iodide rather than chloride or bromide as a counterion to Pd(II) ensured faster reaction rates and better yields in final products. Only traces of thiophenes **2** were obtained when reactions were carried out in the absence of catalyst, with partial decomposition of starting enynethiols **1**. Substrates leading to low-boiling thiophenes were caused to react with PdI₄²⁻ without additional solvent, to facilitate product recovery. In other cases, N,N-dimethylacetamide (DMA) was used as the solvent. This ensured lower viscosity of the medium and better yields in thiophenes (even though the kinetics were slowed). It is conceivable that substrate and/ or thiophene decomposition becomes less favored with dilution.

A likely mechanism for the cycloisomerization process involves the electrophilic activation of the triple bond by Pd(II)[9] followed by intramolecular nucleophilic attack by the −SH group, protonolysis, and aromatization (Scheme 1).

Scheme 1

Since the triple bond necessarily coordinates to Pd(II) at the beginning of the catalytic cycle, a higher reactivity is expected for substrates bearing a less hindered triple bond. This is confirmed by the experimental results. Thus, enyne-thiols bearing an external triple bond were more reactive than analogous substrates substituted at C-5 (compare entry 3 with entries 4 and 5 in Table 1). Analogously, substitution at C-2 rather than C-3 led to a dramatic increase in reaction rates, and the reaction could be carried out at room temperature rather than 100 °C (compare entries 4 and 6). This also ensured a higher product yield, owing to the diminished tendency for decomposition at this temperature. Even substitution at C-1 favored the annulation process (compare entries 1 and 2), probably by the "reactive rotamer" effect.[10] Electronic effects, however, also play a role in determining the reactivity of enynethiols. For example, phenyl rather than alkyl substitution at C-5 led to a faster reaction (compare entries 4 and 5). This could be due to the higher electrophilic character of the triple bond when conjugated to an aryl group, which tends to promote the cyclization step, even though coordination to palladium is conceivably less favored.

To our knowledge, the reaction described here is the first example of a synthesis of substituted thiophenes via a Pd-catalyzed cycloisomerization reaction. Formation of thiophenes through annulation of (Z)-2-en-4-yne-1-thiols bearing an internal triple bond substituted with an alkyl group has been reported to occur under strongly basic conditions using KOBuᵗ in BuᵗOH in the presence of 18-crown-6.[5k] In contrast, the present methodology works catalytically under essentially neutral conditions and can be applied to a variety of enynethiols, including base-sensitive substrates such as those bearing an external triple bond.

Supporting Information Available: Experimental procedures and full characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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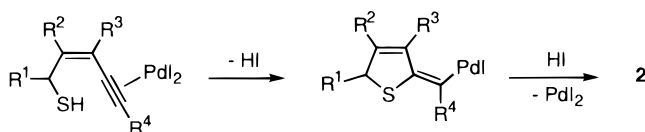
(7) (Z)-2-En-4-yne-1-thiols **1** can be easily prepared by reductive cleavage of the corresponding thioacetates with LiAlH₄, as described in the Supporting Information. The use of DIBAL rather than LiAlH₄ has also been reported.[5k]

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