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3-Phenothiazinyl propiolates – Fluorescent electrophores by Sonogashira coupling of ethyl propiolate

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ABSTRACT

Fluorescent ethyl 3-phenothiazinyl propiolates with reversible Nernstian oxidation potentials were efficiently synthesized by an improved Sonogashira coupling of aryl iodides and ethyl propiolate. The versatility of this modified alkynylation was illustrated by 13 ethyl 3-arylpropiolates in mostly excellent yields with a broad substrate scope. In addition to reversible one-electron oxidations, the title compounds reveal large Stokes shifts, high fluorescence quantum yields, and solvatochromic emission. The photophysical characteristics were corroborated and rationalized by DFT and TD-DFT calculations.

1. Introduction

Phenothiazines bearing conjugated π-substituents in 3- and/or 7-position present interesting classes of functional chromophores [1] that are both luminescent and redox active [2]. In particular, alkynylated phenothiazines [3] have been employed to decorate gold [4] or zinc and iron surfaces [5] with functional reversible redox systems. These systems were readily accessible by Pd-catalyzed alkynylation reactions. However, for synthetic transformations and extended functionalizations, electrophilic three-carbon building blocks such as 3-aryl propiolates, which contain an ester moiety and a conjugated triple bond, are particularly desirable. In heterocycle syntheses, aryl propiolates are for instance particularly valuable as Michael systems [6] or as dienophiles. Most commonly, 3-aryl propiolates are synthesized by the reaction of alkynyl metal species with chloroformates [7]. This methodology, however, only has a limited substrate scope as many functional groups are incompatible with the strongly basic reaction conditions required for the metalation of terminal alkynes. Further limitations arise from the limited availability of the alkyne starting materials. In principle, Sonogashira coupling of aryl halides with alkyl propiolates as alkynyl partner circumvents these problems, thus considerably broadening functional group tolerance and substrate scope. However, electron-poor alkynes such as alkyl propiolates are often less reactive and tend to decompose or undergo self-condensation [8]. In the past years, several approaches have been published that address these issues e. g. by *in situ* generation of alkynylzinc [9] or lithium-indium [10] reagents or by replacement of the aryl halide component by diaryliodonium salts [11] or arylboronic esters [12] To the best of our knowledge, and to our surprise, no direct and general approach to aryl propiolates from aryl halides and alkyl propiolates has been reported to date [13]. We therefore set out to develop a straightforward Sonogashira coupling with ethyl propiolate, compensating its reduced reactivity and diminished stability by carefully adjusting the reaction conditions. In addition, we report the application of this improved methodology to the synthesis of 3-phenothiazinyl ethyl propiolates, interesting novel functional chromophores.

2. Results and discussion

2.1. Synthesis of ethyl aryl propiolates by Sonogashira coupling

For the coupling of aryl iodides **1** a quick screening of the

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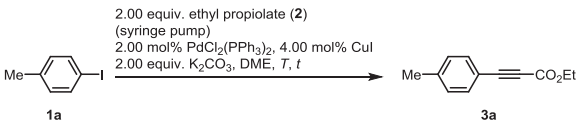
Table 1
Selected optimization reactions for the synthesis of ethyl *p*-tolylpropiolate **3a**.



entry	*T* [°C]	*t* [h]	remark	yield of **3a** (%)[a]
1	90	1		traces
2	40	16		88
3	40	20		96
4	40	20	10 mmol scale	94
5	40	20	without syringe pump	3

[a] Isolated yields after chromatography on silica gel.

stoichiometry, catalyst system, base, and solvent gave the use of 2 equivs of ethyl propiolate (**2**), catalytic amounts of $PdCl_2(PPh_3)_2$ and copper(I) iodide as well as 2 equivs of potassium carbonate in DME as most promising for further optimization studies. As we observed a rapid consumption of ethyl propiolate (**2**) during the course of the reaction, we reasoned that a low stationary concentration by a slow addition of **2** *via* a syringe pump should be beneficial for the coupling product formation. We chose the Sonogashira coupling of 4-iodotoluene (**1a**) with ethyl propiolate (**2**) to give ethyl *p*-tolyl propiolate (**3a**) as a model reaction (Table 1).

While an addition over the course of 1 h at 90 °C gave only traces of the desired product **3a** (Table 1, entry 1), we were delighted to find that decreasing the temperature to 40 °C with a prolonged addition over 16 h already resulted in a yield of 88% of **3a** (Table 1, entry 2). Extending the ethyl propiolate addition to 20 h finally resulted in complete conversion and nearly quantitative isolation of compound **3a** (Table 1, entry 3). The optimized reaction conditions could also be employed on a 10 mmol scale without any significant loss in isolated yield of compound **3a** (Table 1, entry 4). For comparison, the reaction was repeated under the optimized condition without the use of a syringe pump and upon adding the entire amount of ethyl propiolate (**2**) at the beginning of the reaction. This resulted in almost no conversion of **1a** with a drastically reduced yield of **3a** of only 3% (Table 1, entry 5).

With these optimized conditions in hand, we examined the scope of the reaction (Table 2).

To our delight, the functional group tolerance of the reaction proved to be excellent, giving high to nearly quantitative isolated yields for electron-rich (Table 2, entries 1, 4, and 6), electron-poor (Table 2, entries 3, 5, and 10) and sterically hindered substrates (Table 2, entries 6 and 8). The use of 4-iodopyridine (**1g**) resulted in full conversion of the substrate but the desired product **3g** was only isolated in moderate yield, presumably due to the propensity of **3g** for polymerization.

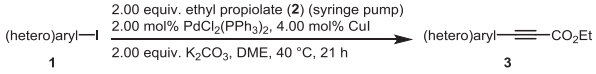
The reaction was additionally employed for the synthesis of phenothiazinyl propiolates, furnishing the desired products **3k** and **3l** in moderate to high yields. In the case of **3l**, the carbon-iodine bond of the bromo-iodo substrate (**1l**) could be selectively addressed, leaving the bromo functionality intact for possible further transformations. Using 3,7-diiodophenothiazine **1m**, phenothiazinyl bis(ethyl propiolate) **3m** was also accessible by double Sonogashira coupling (Scheme 1).

2.2. Photophysical properties of ethyl 3-phenothiazinyl propiolates

The synthesized ethyl phenothiazinyl propiolates **3k**–**m** are yellow in solution and show pronounced fluorescence upon irradiation with UV light (Fig. 1).

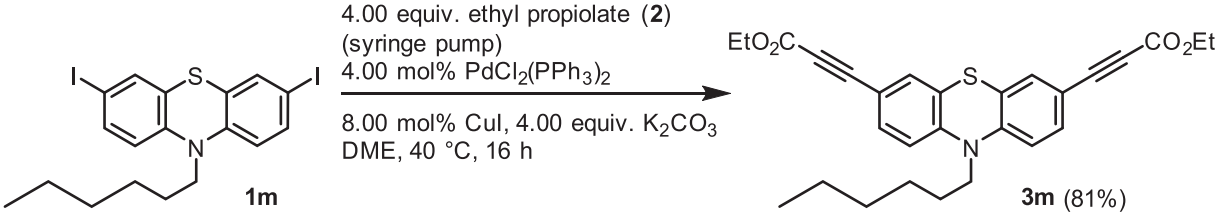
The photophysical properties of all three compounds were studied by absorption and emission spectroscopy in

Table 2
Synthesized ethyl aryl popiolates **3**.



entry	(hetero)aryl iodide 1	yield of propiolate **3** (%)
1	(hetero)aryl = 4-Tol (**1a**)	**3a** (97, 94[a])
2	(hetero)aryl = Ph (**1b**)	**3b** (86)
3	(hetero)aryl = 4-AcC_6H_4 (**1c**)	**3c** (88)
4	(hetero)aryl = 4-$MeOC_6H_4$ (**1d**)	**3d** (97)
5	(hetero)aryl = 4-$F_3CC_6H_4$ (**1e**)	**3e** (83)
6	(hetero)aryl = 2-$MeOC_6H_4$ (**1f**)	**3f** (83)
7	(hetero)aryl = 4-pyridyl (**1g**)	**3g** (50)
8	(hetero)aryl = 9-phenanthryl (**1h**)	**3h** (92)
9	(hetero)aryl = 2-naphthyl (**1i**)	**3i** (96)
10	(hetero)aryl = 3-ClC_6H_4 (**1j**)	**3j** (93)
11	(hetero)aryl = 10-hexyl-10*H*-phenothiazin-3-yl (**1k**)	**3k** (82)
12	(hetero)aryl = 7-brom-10-hexyl-10*H*-phenothiazin-3-yl (**1l**)	**3l** (68)

[a] Prepared on a 10.0 mmol scale.



Scheme 1. Synthesis of diethyl-3,3'-(10-hexyl-10*H*-phenothiazin-3,7-diyl)dipropiolate (**3m**).