Oligoheterocycles by the Stille-coupling reaction.

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Abstract

In this paper the applicability of the Stille-coupling reaction for the synthesis of a variety of oligoheterocyclic compounds is presented. Despite some experimental difficulties (destannylation, purification) we have been able to synthesize a wide variety of compounds based on combinations of pyrrole, thiophene and benzene units in reasonable yields.

Introduction

Since the introduction of the palladium catalyzed coupling reaction between an aryltrialkylstannane and an arylhalide (Stille-coupling) [1] a number of investigations have been presented using this coupling reaction to create all kinds of well-defined oligo-aromatic, poly-aromatic and unsaturated systems [2]. Although the mechanism of this reaction has not been elucidated in detail, it is thought to proceed via a multistep cyclic mechanism [1,3]. One of the major advantages of the Stille-coupling reaction over some other organometallic-coupling reactions is that a wide variety of functional groups on the substrates is tolerated. Therefore, it has also been introduced in heterocyclic chemistry [4–6], particularly in the interesting work of Martina, Enkelmann, Schlüter and Wegner towards the synthesis of well-defined oligo- and poly (pyrrole-2,5-diyl)s [7].

In this paper our investigations of the synthesis of oligoheterocyclic compounds consisting of pyrrole, thiophene, phenylene and ethylene units are presented. Both advantages and disadvantages of the Stille-coupling reaction on these substrates will be discussed.

Results and discussion

The synthesis of oligoheterocycles by the Stille-coupling reaction is exemplified by the synthesis of *N*-*tert*-Butoxycarbonyl-2,5-di[2{5(*N*-*tert*-butoxycarbonyl-5-phenyl-

2-pyrrolyl)thienyl}]-pyrrole (**8**). The total synthesis of compound (**8**) is outlined in scheme 1.

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Scheme 1: Total synthesis of *N*-tert-Butoxycarbonyl-2,5-di[2{5(*N*-tert-butoxycarbonyl-5-phenyl-2-pyrrolyl)thienyl}]-pyrrole (**8**).

In the first step pyrrole is provided with the *tert*-butoxycarbonyl group, which is a well-known *N*-protecting group in pyrrole chemistry [7]. Using 1.2 equivalents of *tert*-butoxycarbonylanhydride *N*-tert-Butoxycarbonylpyrrole (**1**) was isolated as a colourless liquid in high yield (87%) [8]. The next step, a stannylation reaction, is carried out by an indirect lithiation at the 2-position of the protected pyrrole (**1**), using the in-situ prepared lithium-2,2,6,6-tetramethylpiperidide, followed by addition of trimethylstannyl chloride [7c]. After distillation pure *N*-tert-Butoxycarbonyl-2-trimethylstannylpyrrole (**2**) (66%) was obtained as a slightly yellow oil. A Stille-coupling reaction with bromobenzene gave *N*-tert-Butoxycarbonyl-2-phenylpyrrole (**3**) (80%) after column chromatography. Bromination with *N*-bromosuccinimide to form *N*-tert-Butoxycarbonyl-2-bromo-5-phenylpyrrole (**4**) (100%), followed by lithiation (with *n*-butyllithium) and reaction with trimethylstannylchloride, yielded *N*-tert-Butoxycarbonyl-2-trimethylstannyl-5-phenylpyrrole (**5**) (43%).

2,5-Dithienylpyrrole [9], was synthesized via a ring closure reaction of the diketone derivative with ammonium acetate [10]. This compound was protected with the *tert*-butoxycarbonyl-protecting group as described for (**1**) [8] to yield *N*-tert-Butoxycarbonyl-2,5-dithienylpyrrole (**6**) (70%), which was treated with 2.3 equivalents of *N*-bromosuccinimide (optimized conditions) using dichloromethane as a solvent. After two crystallizations *N*-tert-Butoxycarbonyl-2,5-di-5(2-bromothiophenyl)-pyrrole (**7**) (38%) was obtained. We have reason to believe that carrying out the bromination reaction in dimethylformamide (DMF) as a solvent gives better results.

Finally two equivalents of *N*-tert-Butoxycarbonyl-2-phenyl-5-trimethylstannylpyrrole (**5**) were reacted with one equivalent of *N*-tert-Butoxycarbonyl-2,5-di-5(2-bromothiophenyl)-pyrrole (**7**) and after the usual work-up procedures, column chromatography and crystallization, *N*-tert-Butoxycarbonyl-2,5-di[2{5(*N*-tert-butoxycarbonyl-5-phenyl-2-pyrrolyl)thienyl}]-pyrrole (**8**) was obtained in

14% yield as an orange, crystalline solid. This yield seems to be low, but one has to take into account that the reaction was carried out with very small amounts of starting materials (0.5–1.0 mmol scale) and that extensive purification was necessary.

In all the performed coupling reactions destannylated products were observed in the reaction mixture (replacement of the trialkylstannyl group by a hydrogen atom). This was further investigated by taking a standard reaction (the reaction between *N*-tert-Butoxycarbonyl-2-phenyl-5-trimethylstannylpyrrole (**5**) and bromobenzene to form *N*-tert-Butoxycarbonyl-2,5-diphenylpyrrole) and varying the reaction conditions.

Investigating solvent effects in this standard coupling reaction showed that solely a sodium carbonate solution (1M in water) gave almost quantitative yields. By using only an organic solvent like toluene or xylene inferior results were obtained. Using combinations of water or the previously mentioned sodium carbonate solution (sometimes in combination with ethanol) gave mainly the deprotected species, 2,5-diphenylpyrrole. However, when using these optimal conditions for similar coupling experiments, the results were worse (more by-products and slower reactions). Hence it is difficult to draw conclusions about the ideal, general Stille-coupling conditions.

A temperature effect on destannylation was also investigated on the previously mentioned standard coupling reaction. It appeared that under reflux and at room temperature equal amounts of destannylated products were obtained. From this observation it can be concluded that the process of destannylation is not due to a thermal effect.

The Stille-coupling reaction does not only give good results in the coupling reaction towards (**8**), but also towards a number of other compounds, a fraction of which is depicted in scheme 2. A more detailed scope will be presented elsewhere.

for one reaction do not always have to be optimal for comparable reactions.

Experimental

All materials and solvents were of p.a. quality and used as received. For column chromatography Merck silica gel 60 (particle size 0.063-0.200 mm) was used.

NMR spectra were taken on a Bruker AM-400 spectrometer at frequencies of 400.1 and 100.6 MHz. for ^1H and ^{13}C nuclei, respectively. Tetramethylsilane (TMS) was used as an internal standard for ^1H and ^{13}C shifts (ppm) in CDCl_3 .

UV/VIS spectra were taken in acetonitrile as a solvent on a Perkin Elmer Lambda 3B spectrophotometer with wavelengths between 190 and 900 nm.

Infrared spectra were taken on a Perkin Elmer 1600 series FTIR spectrometer with wavenumbers between 4400 and 450 cm^{-1} .

In this section only the Stille-coupling reactions involved in the synthesis of compound (8) are described. All other compounds were synthesized according to literature procedures [7-10].

N-*t*-Butoxycarbonyl-2-phenyl-pyrrole (3)

In a round-bottomed flask (100 ml) toluene (30 ml) and a sodium carbonate solution (1M in water, 30 ml) were added to bromobenzene (3.15 gram, 20.0 mmol) and N-*tert*-Butoxycarbonyl-2-trimethylstannyl-pyrrole (2) (6.62 gram, 20.0 mmol). Upon deaeration and storage under an argon atmosphere, tetrakis (triphenylphosphine) palladium(0) (2 mol%) was added. After heating under reflux for 2 days the mixture was allowed to cool to room temperature. The organic and aqueous layers were separated and the water layer was extracted with Et_2O (3x20 ml). The organic layers were combined, dried with MgSO_4 , filtered and concentrated. Column chromatography of the residue with hexane : dichloromethane = 2:1 as eluent (R_f =0.40) yielded pure N-*tert*-Butoxycarbonyl-2-phenyl-pyrrole (3) (3.91 gram, 16.1 mmol, 80%) as a slightly purple oil.

^1H -NMR (CDCl_3) δ : 7.38-7.26 (m, H-ortho, H-meta, H-para, H-5, 6H), 6.22 (t, J =3.3 Hz, H-4, 1H), 6.18 (dd, J =3.3 and 1.8 Hz, H-3, 1H), 1.33 (s, Boc, 9H).

^{13}C -NMR (CDCl_3) δ : 149.3 (C=O, Boc), 135.0/134.4 (C-2/C-1'), 129.1/127.5 (C-2'/C-3'), 127.1 (C-4'), 122.5 (C-5), 114.3 (C-3), 110.5 (C-4), 83.4 (C-ipso, Boc), 27.5 (Methyl, Boc).

N-*tert*-Butoxycarbonyl-2,5-di[2{5(N-*tert*-butoxycarbonyl-5-phenyl-2-pyrrolyl)thienyl}]pyrrole (8)

In a round-bottomed flask (10 ml) toluene (2 ml) and a sodium carbonate solution (1M in water, 2

Scheme 2: A scope of some synthesized oligoheterocyclic compounds by the Stille-coupling reaction.

Conclusion

Using the Stille-coupling reaction we have been able to synthesize a large number of different oligoheterocyclic compounds. Despite difficult isolation procedures (extraction, column chromatography, crystallization) these compounds were isolated in reasonable yields.

Destannylation was one of the major problems during the synthesis of these oligomers. Investigation of various reaction conditions (e.g. solvent, temperature) allowed optimization of the Stille-coupling reactions. It appeared, however, that the optimal solvent conditions

ml) were added to *N*-*tert*-Butoxycarbonyl-2,5-di-5(2-bromothieryl)-pyrrole (**7**) (0.2429 gram, 0.497 mmol) and *N*-*tert*-butoxycarbonyl-2-phenyl-5-trimethylstannyl-pyrrole (**5**) (0.2429 gram, 1.005 mmol). Upon deaeration and storage under an argon atmosphere, tetrakis (triphenylphosphine) palladium(0) (2 mol%) was added. After heating under reflux for 2 days the mixture was allowed to cool to room temperature. The aqueous and organic layers were separated and the water layer was extracted with Et₂O (3x5 ml). The organic layers were combined, dried with MgSO₄, filtered and concentrated. Column chromatography of the residue with hexane : dichloromethane = 1:1 (*R_f*=0.25) as eluent followed by a crystallization from *n*-hexane yielded pure *N*-*tert*-Butoxycarbonyl-2,5-di[2{5(*N*-*tert*-butoxycarbonyl-5-phenyl-2-pyrrolyl)thienyl}]-pyrrole (**8**) (0.0577 gram, 0.0709 mmol, 14%) as an orange, crystalline solid.

m.p. 122–123 °C.

¹H-NMR (CDCl₃) δ: 7.41–7.28 (m, H^{'''}-ortho, H^{'''}-meta, H^{'''}-para, 10H), 7.08/7.03 (dxd, *J*=3.7 Hz, H-3'/H-4', 4H), 6.37 (d, *J*= 3.6 Hz, H-3'', 2H), 6.35 (s, H-3, H-4, 2H), 6.23 (d, *J*= 3.3 Hz, H-4'', 2H), 1.36 (s, Boc, 9H), 1.22 (s, Boc'', 18H).

¹³C-NMR (CDCl₃) δ: 149.5 (C=O, Boc''), 194.4 (C=O, Boc), 136.7/134.4/134.3/134.0/128.7/128.3 (C-2,C-5/C-2'/C-5'/C-2''/C-5''/C-1'''), 128.3/127.8 (C-2'''/C-3'''), 127.2/127.0/126.6 (C-3'/C-4'/C-4'''), 113.9/113.6/112.1 (C-3/C-4/C-3''/C-4''), 84.6 (C-ipso, Boc), 84.2 (C-ipso, Boc''); 27.2 (Methyl, Boc), 27.1 (Methyl, Boc'').

UV (CH₃CN) λ_{max} 346 nm.

IR (KBr) ν 2978, 1750, 1300, 1141, 842–698 cm⁻¹.

Absorption spectra

Compound (**8**) was deprotected by heating at 185 °C for about 5 minutes under vacuum conditions (evolution of isobutene and carbondioxide). A UV-measurement was taken after making a solution in acetonitrile under inert conditions (glovebox).

λ_{max} (deprotected species) 427 nm.

(λ_{max} (protected species) 346 nm.)

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