A Simple Access to Biologically Important trans-Stilbenes via Ru-Catalyzed Cross Metathesis

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Dedicated to Prof. Herbert Schumann on the occasion of his 70th birthday

Abstract: The cross metathesis of methoxy- or acetoxy-substituted styrenes using the Grubbs II catalyst affords unsymmetrical (mixed) E-stilbenes with astonishingly high selectivity (up to 79% yield). This approach offers a short and flexible synthesis of variously substituted stilbenes, which are derivatives or precursors of biologically important compounds such as resveratrol, piceatannol, and pinostilbene.

Key words: cross metathesis, ruthenium catalysis, resveratrol, stilbenes

In recent years, polyhydroxylated stilbenes such as resveratrol (1a) and piceatannol (1b) have gained tremendous importance especially due to their potential for the prevention and therapy of cancer.1 Compounds of type 1 (R = OH, OMe, or O Gly) have been identified, as metabolites in more than 70 different plant species, as phytoalexin suppressants, for instance, in the growth of pathogenic fungi.2 Moreover, these compounds exhibit a variety of other interesting biological properties including cardiovascular protecting effects.3 Very recently, compound 1e was found to enhance the activity of antibiotics by blocking the efflux pumps of bacterial cells.4

Attempts by Chang et al. to achieve selective cross metathesis between two different styrene derivatives (with electronically different substituents) were reported to produce inseparable product mixtures in 'rather statistical' ratios, and these authors thus concluded that 'this approach is not suitable for obtaining unsymmetrical stilbenes with practical purposes'.12

In the course of our own research in the field of bioactive stilbenes we decided to reinvestigate the possibility of employing cross metathesis (employing the Ru-catalyst 2) for the synthesis of compounds of type 1 with a special focus on methoxy-substituted compounds. As a particularly relevant case, we first studied the reaction between 4-methoxystyrene (5) and 3,5-dimethoxystyrene (6) to give the resveratrol derivative 1e (Scheme 2).

When a solution of styrenes 5 and 6 (1:1) in dichloromethane was heated to 40 °C for 1.5 hours in the presence of 2 mol% of the catalyst 2, we were pleased to find that the desired (mixed) compound 1e was formed as the major product (Table 1, entry 3). According to GC-MS analysis, the crude mixture of metathesis products consisted of 72% of 1e along with 28% of the symmetrical stilbene 7 formed from two molecules of 5.
In a series of further experiments, we varied the ratio of the starting materials in order to probe its influence on the product distribution (Table 1). The best result was obtained when 6 was used in 1.5 fold excess (Table 1, entry 4). As Table 1 also suggests, styrene 5 has a significantly higher tendency (compared to 6) to undergo homo-metathesis, i.e. to form the symmetrical stilbene 7. In contrast, the symmetrical product 8, resulting from ‘dimerization’ of 6, only appeared when this more electron rich styrene was used in excess. At the same time, the formation of 7 (as the faster forming symmetrical by-product) was suppressed in the presence of an excess of 6.

The good selectivity observed with 1.5 equivalents of 6 (Table 1, entry 4) and the fact that products 1e, 7, and 8 are easily separable by flash chromatography indicate that cross metathesis is indeed a very convenient route for the synthesis of 1e (Scheme 1). Repetition of the reaction on a preparative scale (using up to 1 g of 5) afforded the desired product 1e in 76% yield after chromatographic purification.

This very promising result prompted us to address the question whether other unsymmetrical stilbenes could eventually be synthesized in a related fashion. Using a set of seven different styrenes (5, 6, 9, 10, 11, 12, and 13; Figure 2), which are either commercially available or easily prepared from the corresponding aldehydes by Wittig olefination, we then evaluated the scope of the methodology by trying various combinations (Table 2).

All reactions were performed on a 1 mmol scale under the proven conditions (2 mol% of 2, CH₂Cl₂, 40 °C, 1.5 hours). Based on previous experience (Table 1, 1e), the more electron-rich styrenes, e.g. the bis-methoxy compounds 6 and 13, were generally used in excess (1.5 equivalents). Electronically similar styrenes were reacted in a 1:1 ratio. The crude reaction mixture was analyzed by GCMS to determine the product composition before the main product was isolated by flash chromatography.

The structure of the various stilbenes isolated (Figure 3) was confirmed by NMR spectroscopy and MS. In all cases, the E-isomer was formed exclusively within the analytical limits (NMR, GCMS, HPLC). Notably, experiments employing the ortho-methoxy-substituted styrene...
11 did not give any conversion, probably due to the formation of an inactive chelate carbene complex intermediate.\textsuperscript{14}

The structure of compounds 8 and 28 was additionally confirmed by X-ray crystal structure analysis (Figures 4 and 5). Notably, the methoxy substituents are always positioned within the arene plane (\textit{sp}^2 hybridized).\textsuperscript{15}

Figure 5 Structure of compound 28 in the crystalline state.

It should be mentioned that the identity of all products formed in the reactions listed in Tables 1 and 2 was secured by isolation and characterization, and all signals in the GCMS spectra (Figure 6) could be unambiguously assigned by using authentic samples (and by logical analysis of reaction mixtures resulting from different pairs of styrene components).

Figure 6 GCMS analysis of the crude product mixture obtained according to Scheme 2 under the conditions given in Table 1, entry 4.

As the results given in Table 2 clearly demonstrate, the desired mixed (unsymmetrical) metathesis products were formed predominantly in all cases and could be isolated in satisfying yields (62–79%). While the selectivity observed with electronically different starting styrenes was already surprising, the outcome of the reaction between 6 and 13 (1:1 ratio) is particularly remarkable (Table 2, entry 5). Despite the rather small electronic difference between the two components, i.e. 3,4-dimethoxystyrene (6) and 3,5-dimethoxystyrene (13), the cross metathesis product (17) formed more than 70% of the product mixture (while the statistical expected yield would be only 50%).

In conclusion, we have shown that Ru-catalyzed cross metathesis employing the Grubbs-II catalyst opens a very direct synthetic access to a broad variety of unsymmetrically (and symmetrically) substituted \textit{trans}-stilbenes. From an operational point of view, the protocol is particularly attractive because readily available starting materials (styrenes) are reliably converted into valuable products in a single step. At this point it may be worth...
mentioning that the selective cleavage of methoxy groups is possible as we have previously shown for the high yielding conversion of 1e into 1c.1b Thus we are optimistic that the method described in this paper will find application in the search for new oxy-substituted stilbenes with useful biological properties.

All solvents were redistilled. All reactions were carried out under an inert atmosphere of argon. Reactions were monitored by GC-MS using an Agilent Technologies gas chromatograph (GC 6890N) coupled with a mass selective detector (HP 5973N) and an autosampler (HP 7683). Samples were separated on a 30 m x 0.25 mm HP-5 MS column. The column temperature was initially held at 50 °C for 2 min, then the temperature was increased to 300 °C at a rate of 25 °C per min and held at 300 °C for 5 min. The total run time was 17 min. Injector temperature was maintained at 300 °C, and the injection volume was 1.0 µL in the split mode. MS were scanned in the m/z range 35–500 by EI at 70 eV. Flash column chromatography was performed on silica gel (particle size 40–63 µm, Merck). The handling of air-sensitive materials was performed in a glove-box, which was then sealed with a rubber vacuum double manifold and equipped with a reflux condenser un-

| 11C NMR (75 MHz, CDCl3): δ = 55.4 (OCH3), 100.2 (C-4), 104.7 (C-2, C-6), 129.2 (C-7), 139.2 (C-1), 161.0 (C-3, C-5). HRMS: m/z calc for C18H18O3 (M+): 270.1361; found: 270.136.

(E)-1-(4'-Acetoxy phenyl)-2-(3,5-dimethoxyphenyl)ethene (15) Yield: 74%; mp 127 °C (lit.19 128 °C); t9 11.8 min.

1H NMR (300 MHz, CDCl3): δ = 2.29 (s, 3 H, OCH3), 3.84 (s, 3 H, OCH3), 3.64 (t, 1 H, J = 2.1 Hz, H-4), 6.61 (d, 2 H, J = 2.1 Hz, H-2, H-6), 6.77 (dd, 1 H, J = 8.1, 1.5 Hz, H-4), 6.98–7.03 (m, 3 H, H-2’, H-7, H-8), 7.24 (dd, 1 H, J = 8.1, 7.5 Hz, H-5*), 7.04 (d, 1 H, J = 7.5 Hz, H-6*).

13C NMR (75 MHz, CDCl3): δ = 55.2 (OCH3), 105.1 (C-4), 104.6 (C-2, C-6), 121.8 (C-3’, C-5’), 124.7 (C-2’, C-6’), 127.5 (C-1), 139.2 (C-1’), 160.8 (C-3, C-5), 169.5 (C=O). HRMS: m/z calc for C17H18O2 (M+): 298.1205; found: 298.120.

(E)-1-(3'-Methoxyphenyl)-2-(3,5-dimethoxyphenyl)ethene (16) Yield: 77%; oil; t9 11.3 min.

1H NMR (300 MHz, CDCl3): δ = 3.82 (s, 6 H, OCH3), 3.84 (s, 3 H, OCH3), 3.64 (t, 1 H, J = 2.1 Hz, H-4), 6.61 (d, 2 H, J = 2.1 Hz, H-2, H-6), 6.77 (dd, 1 H, J = 8.1, 1.5 Hz, H-4), 6.98–7.03 (m, 3 H, H-2’, H-7, H-8), 7.24 (dd, 1 H, J = 8.1, 7.5 Hz, H-5*), 7.04 (d, 1 H, J = 7.5 Hz, H-6*).

13C NMR (75 MHz, CDCl3): δ = 55.2 (OCH3), 55.3 (2 x OCH3), 100.0 (C-4), 104.6 (C-2, C-6), 111.8 (C-2’), 113.4 (C-4’), 119.3 (C-6’), 128.9 (C-7’), 129.0 (C-8’), 129.1 (C-5’), 138.6 (C-1’), 139.2 (C-1’), 159.9 (C-3’), 161.0 (C-3, C-5). HRMS: m/z calc for C17H18O3 (M+): 270.1256; found: 270.126.

(E)-1-(3’,5’-Dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)ethene (17) Yield: 62%; mp 182 °C (lit.20 182–183 °C); t9 12.0 min.

1H NMR (300 MHz, CDCl3): δ = 3.81 (s, 6 H, OCH3), 3.88 (s, 3 H, OCH3), 3.92 (s, 3 H, OCH3), 6.37 (t, 1 H, J = 2.2 Hz, H-4*), 6.64 (d, 2 H, J = 2.2 Hz, H-2’, H-6*), 6.83 (d, 1 H, J = 7.5 Hz, H-5*), 6.88 (d, 1 H, J = 16.0 Hz, H-7), 7.01 (d, 1 H, J = 16.0 Hz, H-8), 7.02 (dd, 1 H, J = 7.5, 1.8 Hz, H-6), 7.04 (d, 1 H, J = 1.8 Hz, H-2).

13C NMR (75 MHz, CDCl3): δ = 55.3 (OCH3), 55.9 (OCH3), 99.7 (C-4’), 104.3 (C-2’, C-6’), 108.8 (C-2), 111.2 (C-5), 120.0 (C-6), 126.7 (C-8), 128.9 (C-7), 130.9 (C-1), 139.5 (C-1’), 149.0 (C-4), 149.1 (C-4’), 160.9 (C-3, C-5’). HRMS: m/z calc for C18H18O3 (M+): 300.1361; found: 300.136.

(E)-1-(4’-Methoxyphenyl)-2-(3,4-dimethoxyphenyl)ethene (18) Yield: 65%; mp 138 °C (lit.21 135 °C); t9 11.4 min.

1H NMR (300 MHz, CDCl3): δ = 3.81 (s, 6 H, 4’-OCH3), 3.88 (s, 3 H, 3-OCH3), 3.93 (s, 3 H, 4-OCH3), 6.83 (d, 1 H, J = 8.4 Hz, H-5), 6.88 (d, 2 H, J = 8.7 Hz, H-3’, H-5’), 6.91 (s, 2 H, H-7, H-8),
H, HRMS: C-6 127.1 (C-2 13C NMR (75 MHz, CDCl 3): 13C NMR (75 MHz, CDCl 3): 13C NMR (75 MHz, CDCl 3):

Yield: 75%; mp 168 °C (lit.21 169 °C);

Yield: 67%; mp 113 °C;

Yield: 67%; mp 113 °C;

Yield: 75%; mp 168 °C (lit.21 169 °C);

Yield: 65%; mp 144 °C; t<sub>k</sub> 10.5 min.

Yield: 75%; mp 113 °C; t<sub>k</sub> 11.2 min.

Yield: 67%; mp 145 °C (lit.21 145–146 °C); t<sub>k</sub> 11.2 min.

Yield: 75%; mp 123 °C (lit.21 123–124 °C); t<sub>k</sub> 10.0 min.

Yield: 60%; mp 167 °C (lit.25 167–168 °C); t<sub>k</sub> 11.1 min.

1H NMR (300 MHz, CDCl 3): δ = 2.29 (s, 3 H, CH₃), 3.81 (s, 3 H, OCH₃), 6.88 (d, 2 H, J = 8.8 Hz, H-3', H-5'), 7.43 (d, 2 H, J = 8.7 Hz, H-2', H-6'), 7.47 (d, 2 H, J = 8.7 Hz, H-2, H-6).

1H NMR (300 MHz, CDCl 3): δ = 2.29 (s, 3 H, CH₃), 3.81 (s, 3 H, OCH₃), 6.88 (d, 2 H, J = 8.8 Hz, H-3, H-5), 6.93 (d, 1 H, J = 16.0 Hz, H-7), 7.00 (d, 1 H, J = 16.0 Hz, H-8), 7.06 (d, 2 H, J = 8.7 Hz, H-3, H-5), 7.43 (d, 2 H, J = 8.8 Hz, H-2', H-6'), 7.47 (d, 2 H, J = 8.7 Hz, H-2, H-6).

1H NMR (75 MHz, CDCl 3): δ = 21.1 (CH₂), 55.28 (OCH₃), 114.1 (C-3', C-5'), 121.7 (C-3, C-5), 125.5 (C-7), 127.1 (C-2, C-6), 128.4 (C-2', C-6'), 128.4 (C-8), 129.9 (C-1), 135.5 (C-1'), 149.7 (C-4), 159.3 (C-4'), 169.4 (C=O).

HRMS: m/z calcd for C₁₇H₁₈O₃ (M⁺): 268.1099; found: 268.110.

Yield: 113 °C; t<sub>k</sub> 10.7 min.

Yield: 65%; mp 144 °C; t<sub>k</sub> 10.5 min.

Yield: 75%; mp 168 °C (lit.21 169 °C);

Yield: 67%; mp 113 °C;

Yield: 113 °C; t<sub>k</sub> 10.7 min.

Yield: 65%; mp 144 °C; t<sub>k</sub> 10.5 min.

Yield: 75%; mp 168 °C (lit.21 169 °C);

Yield: 67%; mp 113 °C;

Yield: 113 °C; t<sub>k</sub> 10.7 min.

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Note added in proof
References


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