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Synthesis of 1-aryl-1-phenylpropenes using an alkylation-rearrangement-methylation-isomerization one-pot reaction sequence

Research Article

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Abstract: (*Z*/*E*)-1-(2-Methoxyaryl)-1-phenylpropenes have been prepared in good yields by heating a mixture of a phenolic substrate, cinnamyl chloride, tetramethylammonium chloride and K_2CO3 in polyethyleneglycol at 180°C. The one-pot synthesis proceeds through four discrete reaction steps: alkylation of the phenol with cinnamyl chloride, Claisen rearrangement, *O*-methylation and double-bond migration. The configuration of one crystalline product was determined using a single-crystal X-ray diffraction analysis. The thermodynamic and structural features of the products were evaluated using computational chemistry techniques.

Keywords: *Tetramethylammonium • Phenols • Claisen rearrangement • Methylation • Atropisomerism*

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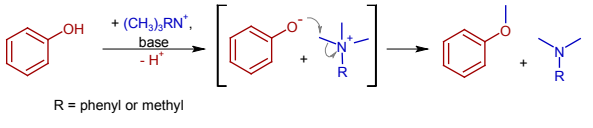
1. Introduction

Quaternary ammonium salts have seldom been used as electrophilic alkylating reagents [1]. Their use for the alkylation of phenols (Scheme 1) was rarely reported, except for the reactions with phenyltrimethylammonium salts, in particular due to their ability to chemoselectively *O*-methylate phenolic substrates containing amino groups [2]. In fact, this methylation method, first described by Rodionov [3], was mainly used in the *O*-methylations of phenolic morphinans [4].

The less reactive tetramethylammonium hydroxide (Me_4NOH) has been used in the methylation of phenolic steroids [5]. We reported a microwave-assisted methylation of phenols with tetramethylammonium chloride (Me_4NCl) in 1,2-dimethoxyethane at 145°C in the presence of K_2CO_3 or Cs_2CO_3 [6]. Recently, a related investigation applying other tetra-alkylammonium salts ($BnEt_3NCl$, $BnEt_3NBr$ and Bu_4NBr), under solventless and microwave-assisted conditions, as well as in acetonitrile, produced similar results [7]. Our next study, on the alkylation of phenols with various tetra-alkylammonium chlorides under conventional heating conditions, demonstrated that relatively high temperatures are required (150–160°C) [8]. Typically, the reactions were conducted in polyethyleneglycol (PEG) using K_2CO_3 as a base.

We thus considered the possible applications that could exploit this lack of reactivity to a synthetic advantage. For this reason we evaluated the ability of tetramethylammonium chloride (Me_4NCl) to *O*-methylate phenols concurrently while they are being formed in a Claisen rearrangement, a [3,3]-sigmatropic reaction, which itself requires comparatively harsh conditions. The thermal variant of the aromatic Claisen rearrangement is most commonly performed at high temperatures, typically 180–225°C, either neat or in high-boiling-point solvents such as *N*,*N*-diethylaniline or diphenyl ether [9]. Most common methylating reagents [10], such as dimethyl sulfate or methyl iodide, are either too reactive or volatile to be applicable at such temperatures.



Scheme 1. General O-methylation reaction of phenols with phenyltrimethylammonium ($PhMe_3N^+$) or tetramethylammonium (Me_4N^+) cations (R is phenyl or methyl).

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2. Experimental Procedure

NMR spectra were recorded at 29°C on a Bruker Avance DPX 300-MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. The melting points were uncorrected and measured on a Kofler micro hot stage. The reactions were monitored with high-performance liquid chromatography (HPLC) using a Nucleosil C-18 column with an acetonitrile/water mobile phase and UV detection at 254 nm. The mass spectra were recorded with a VG-Analytical AutoSpec Q instrument. The elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Potassium carbonate was finely ground and dried at 150°C for 12 hours. Polyethyleneglycol (PEG) with an average molecular mass of 400 was used (PEG400).

All the quantum-mechanical calculations were conducted with the *Gaussian 09* set of programs [11]. Full geometry optimizations with no symmetry constraints on the (*Z*/*E*)-**6a–d** were performed using AM1 semi-empirical quantum chemical calculations. The same method was used for the calculations of fully relaxed single-bond torsional potentials on (*Z*/*E*)-**6a**,**d**; *i.e.*, for each fixed torsional angle around the central, all the remaining internal degrees of freedom were optimized. A rather tight, regular single-bond 10° grid of points was applied in all cases.

Single-crystal X-ray diffraction data were collected at room temperature with a Nonius Kappa CCD diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The data were processed using DENZO [12]. The structures were solved by direct methods implemented in SHELXS-97 [13] and refined by a full-matrix least-squares procedure based on F^2 with SHELXL-97 [14]. All the non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were readily located in difference Fourier maps and were placed at calculated positions and treated using the appropriate riding models. The crystallographic data are listed in Table 1. CCDC-821481 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the synthesis of 1-(2-methoxyaryl)-1-phenylpropenes 6: A stirring slurry of the phenolic compound (**1a–d**; 10 mmol), cinnamyl chloride (**2**; 1.68 g, 11 mmol), tetramethylammonium chloride (2.27 g, 20 mmol) and K_2CO_3 (2.91 g, 20 mmol) in PEG (10 mL) was heated from rt to 180°C during the course of 3 h at a steady rate and then kept stirring at this temperature for 1 h. The mixture was diluted with water (100 mL), extracted with diisopropyl ether (60 mL), the extract was washed with 2M NaOH(aq) (3×50 mL), water (60 mL), filtered through a plug of silicagel and evaporated. This crude product was then purified either by radial chromatography using elution with petroleum ether (**6a–b**) or by crystallizations from methanol or *n*-hexane (**6c–d**). This gave the products (*Z*/*E*)-**6** as 10:1 mixtures of diastereomers (ratios determined by ^{1}H NMR spectroscopy).

Table 1. Crystal data for **6d**.

Parameter	Data
Formula	$C_{20}H_{17}BrO$
***M*$_r$**	353.25
***T* (K)**	293(2)
Crystal system	monoclinic
Space group	P 2_1/n
***a* (Å)**	9.1832(3)
***b* (Å)**	9.6147(3)
***c* (Å)**	18.8861(5)
***β* (°)**	99.599(2)
***V* (Å^3)**	1644.18(9)
Z	4
***D*$_{calc.}$ (Mg m^{-3})**	1.427
***μ* (mm^{-1})**	2.499
F(000)	720
Reflections collected	7203
Reflections unique (R_{int})	3752 (0.0363)
Parameters	201
***R*, w*R*$_2$ [I>2σ (I)]^a**	0.0445, 0.1083
***R*, w*R*$_2$ (all data)^b**	0.0769, 0.1247
GOF, S^c	1.017

$^aR = \Sigma||F_o| - |F_c||/\Sigma F_o|$. $^b wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. $^cS = \{\Sigma[(F_o^2 - F_c^2)^2]/(n/p)\}^{1/2}$ where *n* is the number of reflections and *p* is the total number of parameters refined.

(*Z*/*E*)-1,4-Dimethoxy-2-(1-phenylprop-1-en-1-yl) benzene (6a). Colorless liquid (1.60 g, 63%). IR (NaCl) 1598, 1584, 1495, 1464, 1442, 1418, 1275, 1220 cm^{-1}; MS (ESI) *m/z* 277 (MNa^+), 255 (MH^+), 236, 145, 106, 104; HRMS (ESI) calcd for $C_{17}H_{19}O_2$ $[M+H]^+$ 255.1385, found 255.1376. NMR data for the major(*Z*)-isomer: ^{1}H NMR δ 1.66 (d, *J* = 6.9, 3H), 3.64 (s, 3H), 3.76 (s, 3H), 6.28 (q, *J* = 6.9, 1H), 6.67 (d, *J* = 2.9, 1H), 6.86 (m, 2H), 7.12–7.30 (m, 5H); ^{13}C NMR δ 15.8, 55.9, 56.6, 112.9, 113.3, 117.4, 125.0, 126.3, 126.7, 128.2, 130.1, 138.9, 142.0, 151.8, 153.8. Selected ^{1}H NMR data for the (*E*)-isomer: δ 1.84 (d, *J* = 7.1, 3H), 3.48 (s, 3H), 3.76 (s, 3H), 5.95 (q, *J* = 7.1, 1H).

(*Z*/*E*)-1,2-Dimethoxy-3-(1-phenylprop-1-en-1-yl)-5-propylbenzene (6b). Yellowish liquid (2.00 g, 67%). IR (NaCl) 1581, 1483, 1462, 1424, 1362, 1260, 1232 cm^{-1}; MS (ESI) *m/z* 319 (MNa^+), 297 (MH^+), 179, 131, 117; HRMS (ESI) calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855, found 297.1851. NMR data for the major (*Z*)-isomer: ^{1}H NMR δ 0.94 (t, *J* = 7.3, 3H), 1.63 (m, 2H), 2.54 (t, *J* = 7.6, 2H), 3.50 (s, 3H), 3.86 (s, 3H), 6.25 (q, *J* = 6.9, 1H), 6.52

(d, *J* = 2.1, 3H), 6.71 (d, *J* = 2.1, 1H), 7.25 (m, 5H); ^{13}C NMR δ 14.0, 16.0, 24.8, 38.1, 55.9, 60.5, 111.9, 123.3, 124.8, 126.6, 126.7, 128.2, 133.7, 138.4, 139.2, 142.5, 145.2, 152.9. Selected ^{1}H NMR data for the (*E*)-isomer: δ 0.95 (t, *J* = 7.3, 3H), 1.84 (d, *J* = 7.1, 3H), 3.30 (s, 3H), 3.80 (s, 3H), 5.90 (q, *J* = 7.1, 1H).

(*Z*/*E*)-2,6-Dimethoxy-1-(1-phenylprop-1-en-1-yl) naphthalene (6c). The (*E*/*Z*) mixture was obtained as an amorphous solid that partially crystallized to a white powder over several days (1.70 g, 56%). Mp = 56–66°C; IR (KBr) 1627, 1597, 1507, 1494, 1460, 1422, 1375, 1341, 1253 cm^{-1}; MS (ESI) *m/z* 305 (MH$^+$); HRMS (ESI) calcd for $C_{21}H_{21}O_2$ [M+H]$^+$ 305.1542, found 305.1548. NMR data for the major (*Z*)-isomer: ^{1}H NMR δ 1.51 (d, *J* = 6.9, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 6.57 (q, *J* = 6.9, 1H), 7.00–7.35 (m, 8H), 7.60 (d, *J* = 9.1, 1H), 7.75 (d, *J* = 9.1, 1H); ^{13}C NMR δ 15.7, 55.5, 57.1, 77.2, 106.2, 115.0, 119.6, 123.4, 126.0, 126.1, 126.8, 127.0, 127.8, 128.4, 128.6, 129.0, 130.3, 136.5, 141.8, 152.9, 156.3. Selected ^{1}H NMR data for the (*E*)-isomer: δ 2.02 (d, *J* = 7.1, 3H), 3.71 (s, 3H), 3.93 (s, 3H), 5.80 (q, *J* = 7.1, 1H).

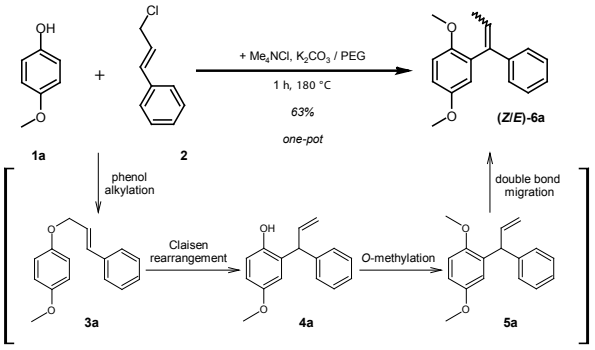
(*Z*)-6-Bromo-2-methoxy-1-(1-phenylprop-1-en-1-yl)naphthalene (6d). The (*E*/*Z*) mixture was obtained as an off-white powder (1.90 g, 54%), which upon recrystallization from *n*-hexane gave the pure (*Z*)-isomer. Mp = 124–127°C; ^{1}H NMR δ 1.49 (d, *J* = 6.9, 3H), 3.80 (s, 3H), 6.57 (q, *J* = 6.9, 1H), 7.17 (m, 5H), 7.35 (d, *J* = 9.0, 1H), 7.39 (dd, *J* = 2.0, 9.0, 1H), 7.56 (d, *J* = 9.0, 1H), 7.76 (d, *J* = 9.0, 1H), 7.96 (d, *J* = 2.0, 1H); ^{13}C NMR δ 15.5, 56.6, 114.8, 117.3, 119.7, 122.8, 125.7, 126.3, 126.7, 127.0, 128.1, 128.2, 129.8, 130.2, 131.5, 135.7, 141.2, 154.3; IR (KBr) 1584, 1494, 1459, 1437, 1333, 1270 cm^{-1}; MS (EI) *m/z*: 354 (M$^+$, 76), 352 (M$^+$, 76), 273 (100), 258 (57), 195 (31), 91 (46), 74 (56); Anal. Calcd for $C_{20}H_{17}BrO$: C 68.00, H 4.85. Found: C 67.99, H 4.90. Selected ^{1}H NMR data for the (*E*)-isomer: δ 2.02 (d, *J* = 7.1, 3H), 3.73 (s, 3H), 5.79 (q, *J* = 7.1, 1H).

3. Results and discussion

Polar and protic solvents were found to enhance the reaction rate of the aromatic Claisen rearrangement [15]. Ethyleneglycol, mono- and diethyl ethers of diethyleneglycol, which are solvents related to PEG, were already found to be efficient, but we could find no examples using PEG for this purpose. Our preliminary experiments with *para*-methyl or *para*-methoxyphenyl allyl ethers confirmed that PEG is an efficient solvent for the Claisen rearrangement when heating the reaction mixture for a minute at 230°C (*para* substitution was preferred in order to avoid the common side products derived from a double [3,3]-sigmatropic rearrangement [9]). Indeed, adding Me_4NCl and K_2CO_3 to the reaction mixture of *para*-methoxyphenyl allyl ether in PEG resulted in the simultaneous *O*-methylation of the Claisen rearrangement product when heating for 3 h at 180°C, but the presence of the base partially caused a double-bond migration in the resulting *ortho*-allylanisole (*e.g.* about half of the product isomerized to the *E*/*Z* mixture of the *ortho*-propenylanisoles). Such a rearrangement-methylation-isomerization sequence could not be optimized to give the *ortho*-methoxy propenylbenzenes as the sole products, because the isomerization step was inefficient and furthermore led to an inseparable mixture of diastereomers.

Such a portion of double-bond migration is surprising considering the relatively low basicity of the K_2CO_3. In our previous work [8], a stronger base like NaOH had to be used at 150°C in PEG for the *O*-methylation of allylphenols like eugenol and 2-allylphenol, when such isomerization was desirable (K_2CO_3 was still ineffective at this temperature). However, we rationalized that if using phenyl cinnamyl ethers as substrates, instead of the plain allyl ethers, the reaction could be more efficient and the isomerization in the last step would be complete: (a) the intermediate ether **3a** rearranges faster [9]; (b) the double-bond isomerization of **5a** should also be considerably easier due to the higher acidity of the benzhydrylic hydrogen in comparison with the benzylic one; (c) the *E* : *Z* ratio could be more biased toward one isomer; (d) and therefore, the reaction should proceed faster toward the end product and thus, overall, be less prone to side reactions.

To further expand the scope of such a one-pot reaction we included the aryl cinnamyl ether formation as the first step of the reaction sequence. Allyl halides like **2** are quite reactive toward phenolates at temperatures much lower than approximately 150°C, as required for the Me_4NCl-based methylation. In this way a complementary use of the two alkylating reagents together in the same reaction mixture is made possible due to their temperature-dependent reactivity. An attempt was thus made by slowly heating a mixture of *para*-methoxyphenol (**1a**), cinnamyl chloride (**2**), Me_4NCl and K_2CO_3 in PEG, from room temperature to 180°C, and keeping it at this temperature for one hour (Scheme 2). The reaction was much cleaner and chromatographic separation gave (*Z*/*E*)-**6a** as a viscous oil. The ratio of diastereomers was 10 : 1, but their configuration could not be unambiguously assigned based on the NMR analysis of the chromatographically inseparable mixture. This same problem was encountered by another group of researchers who obtained an inseparable 85 : 15 mixture of (*Z*/*E*)-**6a** by the $FeCl_3$-catalyzed alkenylation



Scheme 2. An example of the direct synthesis of the 1-(2-methoxyaryl)-1-phenylpropenes directly from a phenol derivative (the brackets show a step-wise representation of the one-pot reaction sequence).

of 1,4-dimethoxybenzene with 1-phenylpropyne [16]. They assigned the major as the (*Z*)-isomer, based on the ^{1}H NMR chemical shift correlation with the software prediction. The same isomer they assigned as (*Z*) was also the major product in our case.

The reaction also performed well on dihydroeugenol (**1b**), 6-methoxy-2-naphthol (**1c**) and 6-bromo-2-naphthol (**1d**) giving the corresponding (*E*/*Z*)-1-(2-methoxyaryl)-1-phenylpropenes **6** (Fig. 1). The isolation of the (*Z*/*E*)-**6c** and (*Z*/*E*)-**6d** required no chromatographic separation as the solid products were obtained by crystallization. A recrystallization of **6d** allowed the isolation of the major diastereomer. Yields of the products **6** were relatively good, ranging from 54 to 67%, representing an average 86–90% yield for each of the four formal reaction steps that together comprise the one-pot reaction sequence. However, some other substrates gave no desired product. For example, *para*-phenylphenol and *para*-cumylphenol gave no expected product as the reaction stopped at their corresponding cinnamyl ethers, thus indicating the reaction conditions were not suitable for the Claisen rearrangement to occur. Some other substrates, like the dihydric phenol naphthalene-2,7-diol, for example, gave complex reaction mixtures.

Having been able to grow crystals of the major diastereomer of the solid product **6d** from *n*-hexane, we determined its structure with a single-crystal X-ray diffraction analysis (Fig. 2). The configuration around the double bond was found to be (*Z*), thus with the methyl and the phenyl groups in *trans* relation. Semi-empirical quantum chemical calculations confirmed that this double-bond configuration is thermodynamically favored; the calculated (*Z*)- *vs.* (*E*)-isomer difference of the ground-state energies was found to be 0.94 kJ mol^{-1} using the AM1 computational model.

No π-π stacking was observed in the crystal packing, but an interesting feature in the molecular structure was the relatively high C2-C3-C10-C11 torsion angle

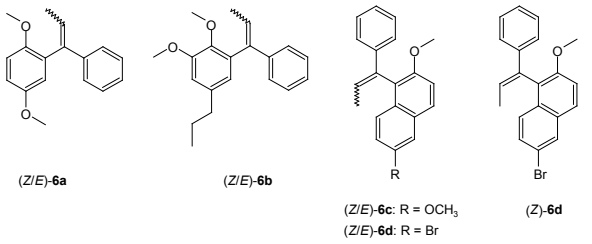


Figure 1. Compounds **6** prepared using the alkylation-rearrangement-methylation-isomerization one-pot reaction sequence.

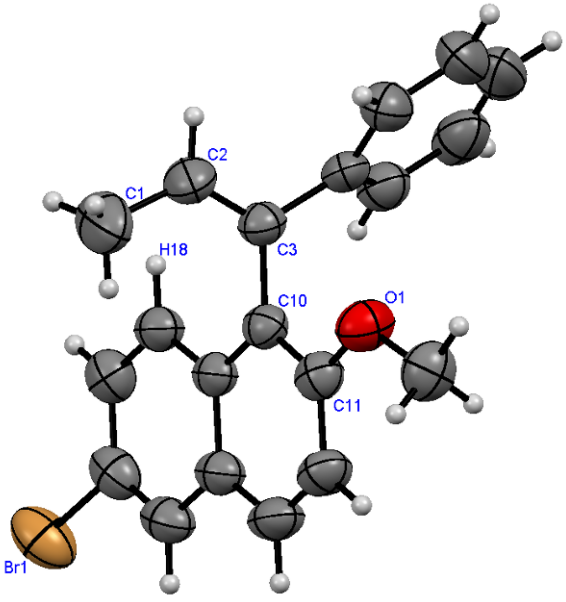


Figure 2. X-Ray crystal structure of (Z)-**6d**.

Φ of 105.42(13)° between the 1-naphthyl and propen-1-yl moieties. This appears indicative of strong steric repulsions, of the methyl (C1) and the phenyl group on the 1-phenylpropene moiety, against the *peri*-hydrogen (H18) and the methoxy group on the naphthyl moiety. It also raised questions about the rotational barrier energy and the possible existence of atropisomerism in (*Z*)-**6d** at room temperature (both enantiomeric rotamers are present in the crystal packing). Published theoretical evaluations demonstrated that 1-vinylnaphthalene already shows a relatively high steric interference at the *peri*-hydrogen of the naphthyl ring [17]. The additional substituents in (*Z*)-**6d** might thus not only prevent the full rotation, but also effectively block the interconversion of the two possible atropisomers.

We thus performed semi-empirical AM1 calculations to obtain an estimation of the pertaining potential energy curve for internal rotation in (*Z*)-**6d**. The results show (Fig. 3) that the compound has a potential energy curve with a minimum energy valley at Φ values from 70° to 100° (the curve is otherwise symmetrical for

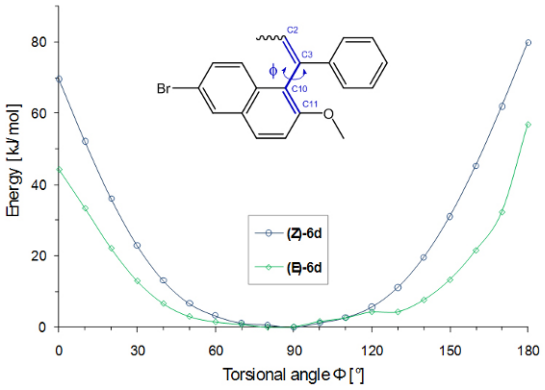


Figure 3. Calculated potential curves for rotation around the C2-C3-C10-C11 torsion angle (Φ) for both diastereomers of **6d** using the AM1 method.

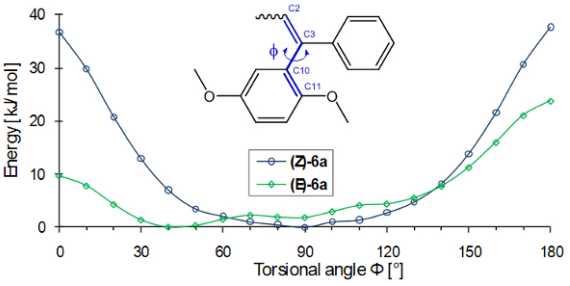


Figure 4. Calculated potential curves for rotation around the C2-C3-C10-C11 torsion angle (Φ) for both diastereomers of **6a** using the AM1 method.

Table 2. Comparison of ^{1}H NMR data for the ethylidene group (=*CH*–*CH*$_3$) of the diastereomers in the mixtures of (*Z*/*E*)-**6**, and their calculated thermodynamic differences.

Reaction product	*Major diastereomer (Z)*			*Minor diastereomer (E)*			Calculated [b] (Z) vs. (E)
	δ [ppm]		$^3J_{HH}$	δ [ppm]		$^3J_{HH}$	ΔE
	CH_3	H	[Hz]	CH_3	H	[Hz]	[kJ mol^{-1}]
6a	1.66	6.28	6.9	1.84	5.95	7.1	-1.20
6b	1.68	6.25	6.9	1.84	5.90	7.1	-2.01
6c	1.51	6.57	6.9	2.02	5.80	7.1	-0.98
6d [c]	1.49	6.57	6.9	2.02	5.79	7.1	-0.94

[a] *Obtained from the NMR analysis of mixtures in $CDCl_3$.*
[b] *The differences of the ground state energies of the (Z)- vs. (E)-isomers as obtained by the AM1 calculations (Austin Model 1).*
[c] *The configuration of the major isomer was confirmed to be (Z) by XRD.*

the enantiomeric rotamers in the interval from 0° to –180°). As expected, there are two maximums in the potential energy, a higher one at 180° (80 kJ mol^{-1}) and a lower one at 0° (70 kJ mol^{-1}). The higher maximum is therefore where the phenyl group is most strongly repulsed by the methoxy group and the methyl group by the *peri*-hydrogen. On the other hand, the repulsion in the opposite rotamer (Φ = 0°) was calculated to be 10 kJ mol^{-1} lower in energy and this maximum thus represents the limiting barrier ΔE_{rot} for the interconversion between the two potential atropisomers. The estimated ΔE_{rot} of 70 kJ mol^{-1} is indicative of a relatively fast axial rotation rate at room temperature, with the interconversion of the order of seconds, which is common for barriers lower than approximately 84 kJ mol^{-1} (20 kcal mol^{-1}) [18]. The results obtained with our calculations do not support the existence of atropisomerism in (*Z*)-**6d**; however, a definitive answer cannot be given, relying solely on semi-empirical calculations.

An analogous calculation for (*E*)-**6d** shows a potential curve with the expected lower maximums (44 and 57 kJ mol^{-1}, respectively).

The potential curves for the (*Z*)-**6a** and (*E*)-**6a** rotations around the corresponding torsion angle are even lower in energy (Fig. 4), which is understandable, because the lack of the *peri*-hydrogen allows for a much freer rotation. The *ortho*-hydrogen thus induces only a much smaller steric repulsion, which is particularly evident from the larger difference in both maximums for (*E*)-**6a**, showing that the repulsion between the methoxy and the phenyl groups is left as the major contributor.

A reliable assignment of the (*Z*)- and (*E*)-isomers comprising the diastereomeric 10 : 1 mixtures of (*Z*/*E*)-**6** using NMR, UV or other spectroscopic techniques is not straightforward without the actual separation of each isomer for their comparison. The XRD data obtained for (*Z*)-**6d** can be considered as further evidence that the other major isomers of the 1-(2-methoxyaryl)-1-phenylpropenes **6** are also of such a configuration. The ^{1}H NMR spectra of the diastereomeric mixtures of the products **6** show a recurring pattern in the chemical shifts and the coupling constant of the methyl group and the hydrogen substituents on the alkene double bonds (Table 2). For the major isomers, the doublet of the methyl group is always upfield (shielded), and the quartet of the hydrogen is always downfield (deshielded), when compared to the chemical shifts of the corresponding signals for the minor isomers. Furthermore, the three-bond coupling constants $^3J_{HH}$ of the major isomers are consistently 6.9 Hz, while the corresponding constants in the minor isomer are consistently 7.1 Hz. The configuration of the major diastereomers was thus assigned to be (*Z*) in all the compounds **6**. In addition, semi-empirical calculations for all the compounds support the notion that all the (*Z*)-isomers show an increased thermodynamic stability.

4. Conclusions

Tetramethylammonium chloride can be used to *O*-methylate *ortho*-allylphenols, as they are formed during the Claisen rearrangement. Double-bond migration occurs due to the basic medium and high

temperature. The substrates for the rearrangement, such as the aryl cinnamyl ethers, can be prepared as part of this one-pot process, thus allowing for a new synthetic method for the preparation of (*Z*/*E*)-1-(2-methoxyaryl)-1-phenylpropenes directly from phenols. The (*Z*) *vs.* (*E*) selectivity in the formation of 1-(2-methoxyaryl)-1-phenylpropenes was 10 : 1 and the stereochemistry assignments were made using XRD (for **6d**) and ^{1}H NMR data. Semi-empirical calculations indicate that the (*Z*)-isomers are the thermodynamically more stable isomers.

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