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Utilization of microwave heating in the McMurry reaction for facile coupling of aldehydes and ketones to give alkenes

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Abstract—Microwave heating was applied in high-yield syntheses of alkenes by McMurry coupling of aldehydes and ketones with low-valent titanium. All aldehydes and ketones including sulfur end-capped analogues gave alkenes in isolated yields above 80% without detectable amounts of pinacols.

Since microwave-assisted organic synthesis was introduced in 1986,[1] applications of microwave heating have been growing steadily.[2] Numerous reactions progress up to 1000 times faster and often cleaner under these conditions compared to conventional heating. In the field of metal catalyzed reactions, huge advances have been achieved by application of microwave heating. Palladium catalyzed reactions,[3] viz. Heck and Sonogashira couplings, in particular have been thoroughly investigated. Shorter reaction times and higher yields compared to conventional heating conditions have often been reported for these reactions.

We focused our attention on the McMurry reaction,[4] which is a useful method for the symmetric coupling of an aldehyde or a ketone to give the corresponding alkene, and we have successfully applied this reaction to syntheses of alkenes from aldehydes and ketones under microwave heating.

During our previous work, especially in the synthesis of double bonds in sulfur end-capped oligophenylene vinylenes (OPVs),[5,6] we used coupling of the corresponding aldehydes and ketones by McMurry reactions. Under conventional heating conditions, the McMurry reaction required heating for several hours for completion. The first step in the McMurry reaction is relatively fast C–C bond formation between the carbon atoms of the two carbonyl groups, formally a pinacol formation. Then on heating for several hours, the double bond is formed; often the alkene is contaminated with traces of pinacol unless purified by chromatography.

In a microwave oven,[7] even low-energy conditions (~10 W) gave complete conversion into the alkene within ten minutes for the McMurry reactions of aldehydes and ketones. The reactions were complete with no sign of starting materials or pinacols[8] by TLC. The results of McMurry couplings performed with microwave heating are summarized in Table 1.[9]

The formation of low-valent titanium by reacting $TiCl_4$ with zinc dust in THF[10] resulted in a grey, almost solid, metallic slurry. The addition of all the $TiCl_4$ was very vigorous, but an advantage of the microwave equipment is that the addition can be performed in a sealed vessel. However, once the entire amount of $TiCl_4$ had been added to the reaction mixture, the metal slurry was easy to handle. The aldehyde or ketone could be added shortly after complete addition of the entire amount of all the $TiCl_4$. After microwave heating for less than a minute, the grey metal slurry turned into a purple slurry appearing almost like a homogeneous solution.

In accordance with conventional heating, only *trans*-stilbenes were produced by the microwave assisted McMurry reactions. In this context, *trans*-stilbene **2**, *trans*-4,4′-dimethylstilbene **4**, and *trans*-4,4′-bis(*tert*-butylthio)stilbene **6**, were prepared from benzaldehyde **1**, 4-tolualdehyde **3**, and 4-(*tert*-butylthio)benzaldehyde **5**, respectively (entries 1–3 in Table 1). We have previously coupled protected sulfur end-capped aromatic

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Keywords: McMurry reactions; Microwave-assisted synthesis; Alkenes; Protected thiols.

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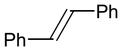
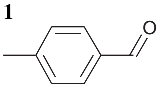
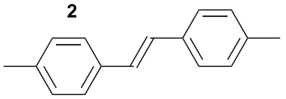
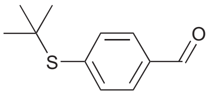
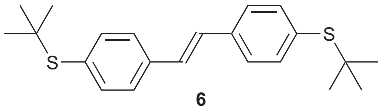
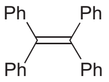
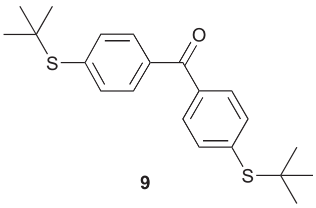
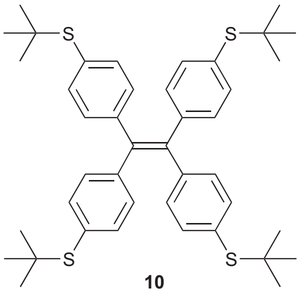
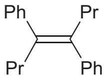
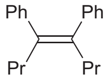
Table 1. Synthesis of alkenes from aldehydes or ketones by microwave assisted McMurry coupling

Entry	Substrate	Product	Yield
1	PhCHO **1**	 **2**	93[a]
2	 **3**	 **4**	91[a]
3	 **5**	 **6**	87[a]
4	PhCOPh **7**	 **8**	96[a]
5	 **9**	 **10**	82[b]
6	PhCOPr **11**	 +  **12a** : **12b** (9 : 1)	93[b]

Aldehyde or ketone $\xrightarrow[\text{MW,110 °C,10 min}]{\text{Low valent Ti, THF}}$ alkene.

[a] Isolated yield.

[b] Yield after recrystallization.

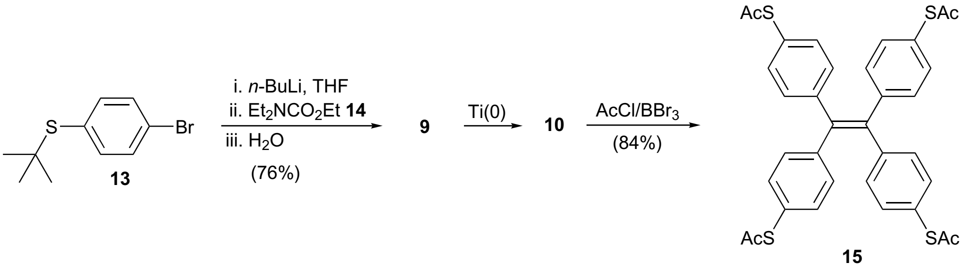
aldehydes using low-valent titanium under conventional conditions. Microwave heating produced **6** from **5** in a higher yield and much faster compared to the conventional reaction without damaging the *tert*-butyl sulfur protecting group.

The McMurry coupling of ketones was found to be a very slow reaction requiring days under conventional conditions. However, using even low-energy microwaves ketones coupled rapidly. This was exemplified by coupling benzophenone **7** and 4,4′-bis(*tert*-butylthio)benzophenone **9** into tetraphenylethylene **8** and tetrakis-[4-(*tert*-butylthio)phenyl] ethylene **10**, respectively (entries 4 and 5 in Table 1). In the latter example, the *tert*-butyl moiety remained unaffected under the McMurry conditions (cf. the synthesis of **6**). To the best of our knowledge, **10** is the first example of a protected thiol end-capped tetraphenylethylene with four sulfur terminals.

The McMurry coupling of butyrophenone **11** was supposed to produce only the *E*-alkene in accordance with the results obtained for aromatic aldehydes. However, this substrate gave a 9:1-ratio of the *E*- and the *Z*-alkenes, **12a** and **12b** (entry 6 in Table 1). This result may be due to the higher steric influence of the propyl group. Simple aliphatic aldehydes and ketones, such as pentanal and cyclohexanone, did not give well-defined reactions.

The bis-thiol end-capped benzophenone protected with *tert*-butyl groups, 4,4′-bis(*tert*-butylthio)benzophenone **9**, was prepared by lithiation of bromophenyl *tert*-butyl sulfide **13** with *n*-butyllithium followed by reaction with ethyl *N*,*N*-diethylcarbamate **14**[11] (Scheme 1).[12] By analogy with similar procedures,[13] **14** was applied in the ketone synthesis due to easy access to precursors of **14**. By reacting *N*,*N*-diethylcarbamoyl chloride with ethanol, **14** was readily prepared.[14] The synthesis of **9** demonstrates the stability of the *tert*-butyl thiol protecting group toward lithium reagents.

After the conversion of **9** into the tetraphenylethylene **10**, smooth deprotection–reprotection was performed by treatment with acetyl chloride and boron tribromide following our procedure[5] for in situ conversion of *tert*-butyl sulfides into the corresponding acetylthio compounds. Conversion of **10** into tetrakis-[4-(acetylthio)phenyl]ethylene **15**[15] was performed in order to obtain intermediates with protected thiol terminals, which are readily cleavable in situ during self-assembly viz. at gold contacts.[16]



Scheme 1.

The novel, acetyl protected, four terminal tetraphenylethylene thiol **15** has been incorporated in our recent work as a component in molecularly based nanoscale electronic devices. Due to its rigidity, **15** might be applied to fixation of a gold cluster at each of the four terminals.[17] Electron transport studies on **15** will be the subject of future investigations similar to those recently carried out on OPVs.[18]

In summary, we have extended the use of microwaves in organic synthesis to the McMurry reaction. Utilizing microwave conditions, the McMurry reactions were complete within 10 min. This method has been employed in the synthesis of two- and four-terminal molecular wires for molecular electronics.

Acknowledgements

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12. Procedure for the synthesis of **9**: 4-Bromophenyl *tert*-butyl sulfide **13** (34.3 g, 140 mmol) was added dropwise under an argon atmosphere to a solution of *n*-butyllithium (2.5 M in hexanes, 70 mL, 70 mmol) in THF (100 mL) cooled in a dry ice/acetone bath. After stirring the reaction mixture at −78 °C for 15 min, ethyl *N*,*N*-diethylcarbamate **14** (10.2 g, 70 mmol) was added over a 10-min period in a dropwise fashion. The reaction mixture was stirred at room temperature for 30 min and then poured into ice (300 g). THF was gently removed on a rotary evaporator and a white product was filtered off and dried in a vacuum oven (1mmHg, 100 °C). Recrystallization from heptane afforded **9** (19.1 g, 76%) as white needles. Mp: 152–153 °C. Anal. Calcd for $C_{21}H_{26}OS_2$: C, 70.35; H, 7.31; S, 17.88. Found: C, 70.29; H, 7.30; S, 17.93. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 18H), 7.64 (d, $J = 6.4$ Hz, 4H), 7.75 (d, $J = 6.4$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.99, 46.76, 129.72, 136.52, 136.95, 138.66, 195.52. MS (EI, 70 eV) *m*/*e* (relative intensity): 358 (M^+, 8), 302 (16), 246 (100).
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14. Procedure for the synthesis of **14**: Diethylcarbamoyl chloride (21.1 g, 200 mmol) was added to a cooled mixture of triethylamine (50 mL) and absolute ethanol (200 mL) over a 10-min period in a dropwise fashion. The reaction mixture was stirred at room temperature for 2 h and then poured into ice (600 g) and extracted with pentane (3 × 100 mL). The pooled organic phases were washed with water (15 mL), dried with $MgSO_4$, filtered, and concentrated by rotary evaporation (30 °C, 20mmHg). Bulb-to-bulb distillation (12mmHg, 100 °C) afforded **14** (16.8 g, 58%) as a colorless liquid. Purity >98% (GC–MS). MS (EI, 70 eV) *m*/*e* (relative intensity): 145 (M^+, 4), 135 (50), 120 (71), 100 (100).
15. Procedures for the synthesis of **15**: To a solution of **10** (0.69 g, 1 mmol) and acetyl chloride (2 mL) in dichloromethane (15 mL) was added boron tribromide (1.0 M solution in dichloromethane, 4.4 mL, 4.4 mmol). The resulting dark-colored solution was stirred under nitrogen

for 2 h at room temperature and then poured into ice (100 g). After the separation of the phases, the water phase was extracted with toluene (3 × 20 mL). The pooled extracts were dried with magnesium sulfate, filtered, and evaporated. The product was separated by flash chromatography on silica gel 60F (20 g) by means of dichloromethane. After evaporation, recrystallization from toluene–heptane (1:3) afforded **15** (0.53 g, 84%) as off-white crystals. Mp: 172–173 °C. Anal. Calcd for $C_{34}H_{28}O_4S_4$: C, 64.94; H, 4.49; S, 20.39. Found: C, 64.96; H, 4.46; S, 19.99. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 12H), 7.05 (d, $J = 8.4$ Hz, 8H), 7.18 (d, $J = 8.4$ Hz, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.04, 126.76, 131.83, 133.68, 140.69, 143.50, 193.62. MS (EI, 70 eV) *m*/*e* (relative intensity): 628 (M^+, 100), 586 (32), 544 (24).

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