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Microwave-assisted $InCl_3$-catalyzed Meyer–Schuster rearrangement of propargylic aryl carbinols in aqueous media: a green approach to α,β-unsaturated carbonyl compounds

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ABSTRACT

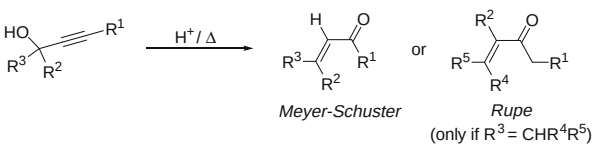
A novel, efficient, simple and environmentally benign protocol for the Meyer–Schuster isomerization of propargylic aryl carbinols into α,β-unsaturated carbonyl compounds has been developed using catalytic amounts of $InCl_3$, pure water as the solvent, and microwave irradiation as the heating source.

The use of water as an eco-friendly reaction medium in conjunction with microwave (MW) irradiation is gaining widespread acceptance, not only because particular or unexpected reactivities can be in some cases observed, but also because its significant usefulness for Green Chemistry.[1] Similarly, the search of organic reactions proceeding with atom-economy (all atoms of reactants end up in the final products) has also emerged as a major objective for synthetic chemists.[2] In this context, the broad utility of α,β-unsaturated carbonyl compounds and the easy preparation of propargylic alcohols make the isomerization of the latter into the former a useful transformation.[3] To achieve this goal, the well-known Meyer–Schuster rearrangement represents the simplest and most widely used approach (Scheme 1).[4,5]

Successful application of this Brønsted acid-catalyzed isomerization reaction in the design of novel histamine H_3-receptor antagonists,[6] antifungal mold metabolites[7] and aza-analogues of the biological active Senkyunolide-E,[8] as well as in the construction of the Taxol AB-system,[9] has been described confirming its synthetic utility. However, harsh conditions and strong acidic media are usually required, which often give rise to non-regioselective transformations due to competitive Rupe-type processes (Scheme 1),[5] limiting seriously the applicability of this textbook reaction.

In recent years, it has been described that regioselective Meyer–Schuster reactions can be efficiently achieved under milder conditions by the aid of transition metals, the reported examples including several oxo-complexes[10] as well as Ru-,[11] Au-[12] and Ag-based[13] systems. In addition, taking advantage of the affinity shown by 'soft' Lewis-acids for π-bonds over non-bonded electron pairs,[14] Dudley and co-workers have also demonstrated the utility of such reagents (i.e., $InCl_3$, $Sc(OTf)_3$ and $Cu(OTf)_2$) as catalysts for the Meyer–Schuster isomerization of ethoxyalkynyl carbinols into α,β-unsaturated esters.[15]

In all the above-mentioned examples the reactions were performed in organic media, the search for alternative catalytic methods operating in water being highly desirable.[16] In this sense, we report herein an efficient, general and environmentally benign aqueous protocol for the Meyer–Schuster isomerization of propargylic aryl carbinols into α,β-unsaturated carbonyl compounds



Scheme 1. The Meyer–Schuster and Rupe rearrangements.

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Table 1
MW-assisted $InCl_3$-catalyzed Meyer–Schuster rearrangement of terminal propargylic aryl carbinols[a]

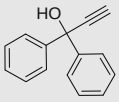
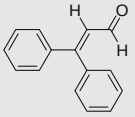
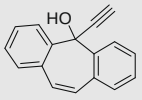
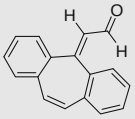
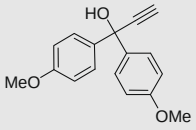
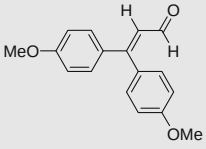
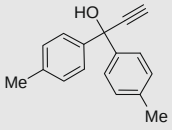
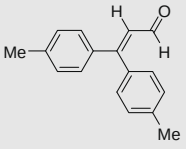
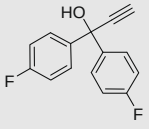
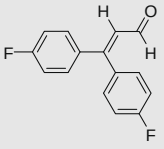
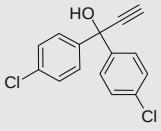
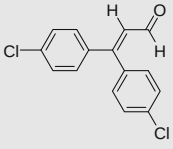
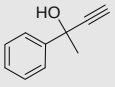
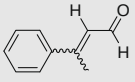
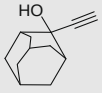
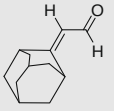
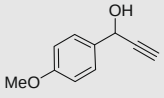
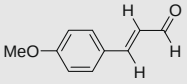
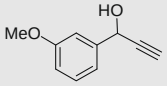
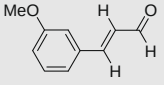
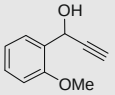
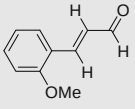
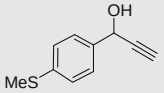
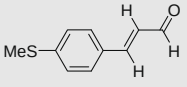
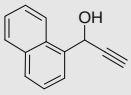
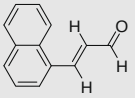
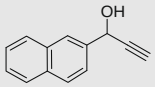
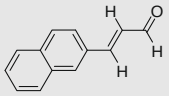
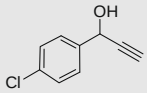
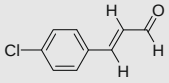
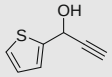
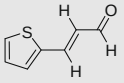
Entry	Propargylic alcohol	% $InCl_3$ (mol %)	Time (min)	Product	GC yield (%)	Isolated yield (%)
1		1	5		>99	91
2		1	5		>99	87
3		1	5		>99	93
4		1	15		>99	89
5		1	30		>99	90
6		1	150		>99	93
7		1	5		>99	90[b]
8		5	300		96	85
9		1	10		>99	92
10		2	180		97	86
11		1	10		98	88
12		1	10		97	91
13		1	120		97	84

Table 1 (*continued*)

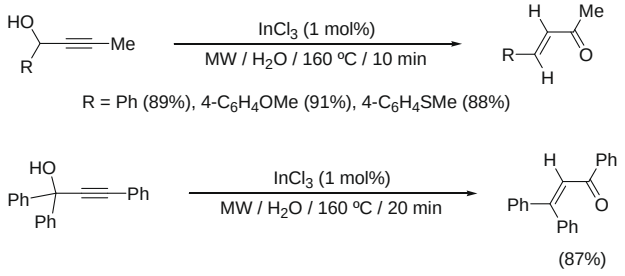
Entry	Propargylic alcohol	% InCl3 (mol %)	Time (min)	Product	GC yield (%)	Isolated yield (%)
14		2	120		99	90
15		2	360		94	81
16		1	10		>99	95

[a] Reactions were performed under air atmosphere in a CEM Discover® S-Class microwave synthesizer at 160 °C through moderation of the initial microwave power (300 W); 1 mmol of the corresponding propargylic aryl carbinol (1 M in water) was used.
[b] Isolated as a mixture of stereoisomers (*E*/*Z* ratio = 61:39).

using catalytic amounts of the water-compatible and inexpensive Lewis-acid $InCl_3$. Microwave irradiation is used as the heating source resulting in short reaction times, almost quantitative yields and complete *E*-stereoselectivity. Results obtained in the isomerization of a variety of terminal propargylic aryl carbinols are summarized in Table 1.

At the beginning, the isomerization of commercially available 1,1-diphenyl-2-propyn-1-ol into 3,3-diphenylpropenal was used as a model reaction. Thus, we found that, under optimized conditions (1 mol % $InCl_3$; 1 M solution of the substrate in water, 160 °C), complete and selective conversion of the alkynol into the enal takes place after only 5 min of MW-irradiation (entry 1), the use of lower temperatures and/or catalyst loadings slowing down the reaction considerably.[17] Remarkably, neither an inert atmosphere nor an organic co-solvent was required. Under these optimal reaction conditions,[18] other tertiary propargylic aryl carbinols were efficiently transformed into the corresponding enals (⩾87% isolated yields; quantitative yields were in all cases observed by GC) within 5–150 min (entries 1–7). Influence of the electronic properties of the aryl rings on the reaction rates was observed. Thus, alkynols with electron-withdrawing groups showed less reactivity (entries 5–6) as compared to the substrates with electron-donating functionalities (entries 3–4). Interestingly, no competitive Rupe-type rearrangement of 2-phenyl-3-butyn-2-ol was observed under these conditions, a mixture of the *E* and *Z* stereoisomers of 3-phenyl-2-butenal being exclusively formed (entry 7).[19] As shown in entry 8, $InCl_3$ is also able to catalyze the isomerization of the dialkyl-substituted alkynol 2-ethynyl-adamantan-2-ol in water. However, a higher catalyst loading (5 mol %) and a longer reaction time (5 h) were in this case required.

Probably, the most significant results of this study were obtained in the isomerization of secondary terminal alkynols (entries 9–16), since the resulting enals were generated in all cases as the thermodynamically more stable *E* isomer, regardless of the electronic properties of the aromatic or heteroaromatic substituent present in the molecule. Such a remarkable stereoselectivity has been rarely observed.[10b,12d,19]



Scheme 2. Meyer–Schuster isomerization of internal alkynols.

Finally, it is also worth to note that the scope of this aqueous isomerization process is not restricted to propargylic aryl carbinols bearing a terminal C≡C bond, the internal ones being also efficiently transformed into the corresponding enones. Moreover, as exemplified in Scheme 2, complete *E*-stereoselectivity was once again reached starting from secondary alcohols.

In summary, a simple, general,[20] selective and efficient protocol for the the Meyer–Schuster isomerization of propargylic aryl carbinols into α,β-unsaturated carbonyl compounds, very valuable raw materials in organic synthesis, has been developed using inexpensive $InCl_3$.[21] Moreover, the process is truly sustainable since, in addition to its atom-economy, it proceeds in a pure aqueous medium, employs MW-irradiation as the heating source, and the catalyst can be recycled.[22] Further investigations into the application of this methodology to more challenging substrates, as well as in the development of sequential C–C coupling processes,[23] are now in progress in our laboratories.

Acknowledgments

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16. Uncatalyzed Meyer–Schuster rearrangement of 2-phenyl-3-butyn-2-ol into (*E*/*Z*)-3-phenyl-2-butenal (34% yield after 1 h) under high-temperature neutral aqueous conditions (200 °C) has been described: An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505–2511.
17. (a) As an example, using 1 mol % of $InCl_3$ at 100 °C, complete conversion of 1,1-diphenyl-2-propyn-1-ol into 3,3-diphenylpropenal was only achieved after 24 h of MW-irradiation. (b) It must also be noted that conventional instead of MW-heating was found to be much less effective (34% yield after 24 h at 100 °C using 1 mol % of $InCl_3$). (c) As expected, no isomerization of 1,1-diphenyl-2-propyn-1-ol takes place in the absence of $InCl_3$ (160 °C under MW-irradiation).
18. Typical experimental procedure: A pressure-resistant septum-sealed glass microwave reactor vial was charged with the corresponding propargylic aryl carbinol (1 mmol), $InCl_3$ (1–5 mol %), a magnetic stirring bar and water (1 mL). The vial was then placed inside the cavity of a CEM Discover® S-Class microwave synthesizer and power was held at 300 W until the desired temperature was reached (160 °C). Microwave power was automatically regulated for the remainder of the experiment to maintain the temperature (monitored by a built-in infrared sensor). The internal pressure during the reaction ranged between 10 and 90 psi. After completion of the reaction (see Table 1 and Scheme 2), the vial was cooled and the organic product was extracted with diethyl ether (15 mL). After drying with $MgSO_4$, the solvent was evaporated under vacuum, and the crude residue was purified by flash chromatography over silica gel using EtOAc/hexane (1:10) as a eluent. The identity of the resulting carbonyl compounds was assessed by comparison of their ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data with those reported in the literature and by their fragmentation in GC/MS.
19. See, for example: Cadierno, V.; García-Garrido, S. E.; Gimeno, J. *Adv. Synth. Catal.* **2006**, *348*, 101–110.
20. The only limitation of this method concers the use of primary propargylic alcohols. Thus, while the internal alkynols $RC{\equiv}CCH_2(OH)$ (R = Ph, *n*-Bu) remained unreacted after 3 h of MW-heating in the presence of $InCl_3$ (1 mol %), propargylic alcohol itself led to a polymeric material formation.
21. One referee suggested a hypothetical reaction sequence involving an initial *anti*-Markovnikov C≡C hydration to form a β-hydroxy aldehyde, followed by thermal elimination of water under MW-irradiation. Such a possibility has been discarded since no aldehyde intermediates were detected by monitoring the course of the reactions by GC/MS. A classical Meyer–Schuster reaction pathway involving indium-hydroxo derivatives is therefore proposed.
22. After a simple extraction of the final product with diethyl ether, the aqueous phase containing the catalyst can be re-used in at least two consecutive runs with only a slight decrease in the activity. For example, using the isomerization of 1,1-diphenyl-2-propyn-1-ol into 3,3-diphenylpropenal as model reaction, >99% GC conversion was achieved in the third cycle after 20 min of MW-heating (to be compared with entry 1 in the table).
23. Cadierno, V.; Díez, J.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. *Adv. Synth. Catal.* **2006**, *348*, 2125–2132.