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LETTER

Microwave-assisted efficient thiolate-catalysed homo- and crossed intermolecular Tishchenko reactions†

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Recently, the first efficient intermolecular crossed Tishchenko reactions were reported. The utility of these processes is curtailed by long reaction times of up to 4 days (at reflux). Herein we report that these reactions are highly susceptible to acceleration by microwave irradiation—allowing fast, efficient, high-yielding coupling to proceed in 10–180 min.

The Tishchenko reaction[1,2] is a hydride-transfer mediated process related to (but potentially more synthetically useful than) the Cannizzaro reaction,[3] where two aldehyde molecules can undergo disproportionation, with subsequent coupling to form a single ester product. This intriguing aldehyde-to-ester transformation reaction has been known for over a century, yet few practical applications of the process have been developed and it is little-used as a synthetic strategy by contemporary chemists.[4]

There are several limitations which have curtailed the utility and applicability of the reaction: several metal-based catalytic systems for promoting the reaction have been devised,[5–10] however the reaction is of poor substrate scope: only 'dimerisation' of aldehydes was possible, yields of homo-Tishchenko esters using substituted benzaldehyde substrates are often variable and until recently the coupling of aldehydes to ketones (in an intermolecular context) was unknown.[4]

Recently—inspired by the mode of action of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase[11–13]—we developed the first thiol(ate) catalysed Tishchenko reactions.[14] The catalysts required are simple, inexpensive thiols, used in the presence of a Grignard reagent base.[15] Homo-Tishchenko reactions involving either benzaldehyde or (significantly) substituted analogues proceeded in good–excellent yields with 5–20 mol% catalyst loading (Fig. 1).

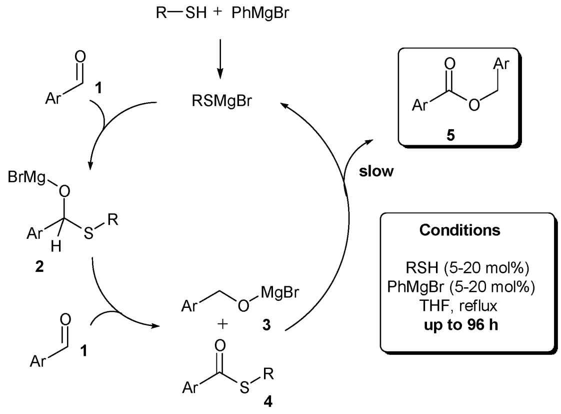

Fig. 1 The thiolate catalysed homo-Tishchenko reaction.

Perhaps more significantly, considerable direct evidence supporting the proposed reaction mechanism involving **2–4** as intermediates (Fig. 1) and a slow acyl-transfer step was obtainable by ^{1}H NMR spectroscopy. This mechanistic information subsequently guided the development of thiol precatalysts tailored to promote the first selective intermolecular[16] crossed-Tishchenko reactions between aldehydes and activated ketones.

The major drawback associated with this protocol was the reaction rate—the reaction must be held at reflux temperature for prolonged times: up to 4 days for cases involving recalcitrant substrates. Cognisant of the impact long reaction times will have on the widespread applicability and utility of the reaction, we embarked on a programme aimed at increasing the reaction rate without resorting to the use of impractical catalyst loadings.

The reaction is most efficient in ethereal solvents (THF was identified as the optimal medium studied in our initial investigations);[17] thus we attempted to carry out the process in higher boiling ethers such as 2-methyltetrahydrofuran and 1,4-dioxane (at reflux), without observing any rate acceleration.

It was next decided to investigate the effect of microwave radiation on the process. The results of our preliminary experiments involving the microwave-aided homo-Tishchenko reaction are outlined in Table 1.

We were very pleased to observe significant rate accelerations on irradiating to a maximum reaction temperature of 110 °C

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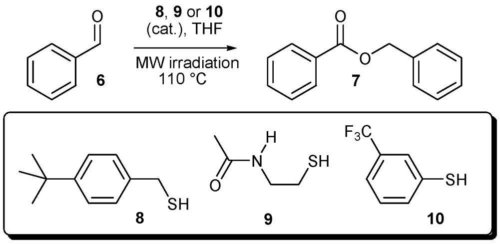
† Electronic supplementary information (ESI) available: General experimental procedures, ^{1}H and ^{13}C NMR spectra for all crossed products, characterisation data for all new products. See DOI: 10.1039/c0nj00790k

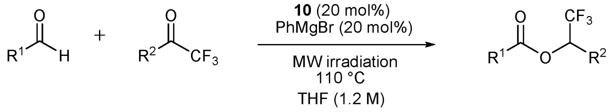
Table 1 Microwave-assisted homo-Tishchenko reactions

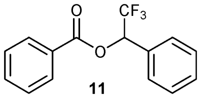
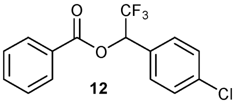
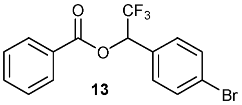
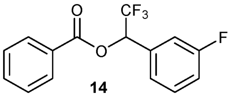
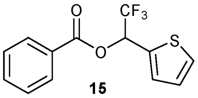
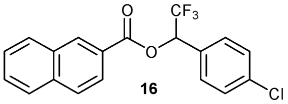
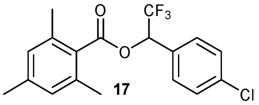
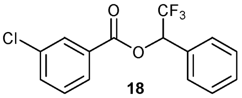
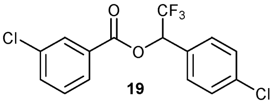
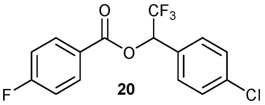
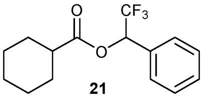
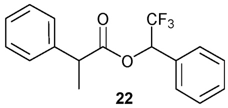


Entry	Catalyst	Loading/mol%	Conc./M	Time/min	Yield^a (%)
1	**8**	10	0.68	10	70
2	**9**	10	0.68	10	64
3	**10**	10	0.68	10	28
4	**8**	10	1.0	10	85
5	**8**	10	1.2	10	83
6	**8**	10	1.2	30	82
7	**8**	10	1.8	10	85
8^b	**8**	5	1.8	30	92 (90)
9	**8**	5	1.8	10	85
10	**8**	5	2.0	30	91

^{a} Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. ^{b} Isolated yield in parenthesis.

Table 2 Microwave-assisted intermolecular crossed-Tishchenko reactions



Entry	Product	Time/h	Yield^a (%)
1	 **11**	3	82
2	 **12**	3	81
3	 **13**	3	81
4	 **14**	3	63
5	 **15**	3	51^b
6	 **16**	3	68
7	 **17**	3	0
8	 **18**	2	73
9	 **19**	3	83
10	 **20**	3	76
11	 **21**	3	56^c
12	 **22**	3	34^{c,d}

^{a} Isolated yields. ^{b} Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. ^{c} Using 2.0 equiv. of the ketone. ^{d} Isolated as a 4 : 1 mixture of diastereomers.

under conditions otherwise identical to those used in the original study.[14,18] Under these conditions 4-*tert*-butylbenzylmercaptan (**8**—at 10 mol% levels) could promote the formation of benzyl ester **7** from benzaldehyde (**6**) in good yield in only 10 minutes (entry 1). As expected, catalysts **9** and **10**, which previously proved useful in the catalysis of *crossed* Tishchenko reactions, were less effective here (entries 2–3).[19]

We next set about optimising the conditions associated with the microwave-mediated process. Increasing the reaction concentration (a desirable modification in its own right) resulted in a marked improvement in product yields: a concentration of 1.0–1.2 molar allowed the formation of **7** in yields $>80\%$ (entries 4–6), while using 1.8–2.0 M reaction concentrations makes the isolation of **7** in $>90\%$ yield possible after 30 minutes reaction time with a reduced catalyst loading of 5 mol% (entries 7–10). It is noteworthy that a minimum of 10 mol% catalyst loading was required to achieve a product yield of $>90\%$ in the corresponding thermal process reported previously.[14] Attempted reactions at concentrations higher than 2.0 M led to poor solubility and inconsistent results.

Attention now turned to the more challenging crossed-Tishchenko process (Table 2). In these reactions, acyl-transfer between the thioester intermediate and the ketone-derived alkoxide (after hydride transfer) is rate-determining; therefore use of the substituted thiophenol catalyst **10** (which results in a more electrophilic thioester intermediate which undergoes more rapid acyl-transfer) is required. Treatment of a 1 : 1 mixture of benzaldehyde and 2,2,2-trifluoromethylacetophenone in THF under microwave irradiation in the presence of **10** (20 mol%) resulted in the formation of the coupled product **11** in high yield (entry 1) after only 3 hours. The reaction proceeded chemoselectively—^{1}H NMR spectroscopic analysis did not detect any homo-Tishchenko product (*i.e.* **7**) in the crude reaction mixture.

Benzaldehyde could also be reacted with halo-substituted activated ketones to furnish **12–14** without difficulty (entries 2–4). The (relatively) deactivated 2-thiophenyl substituted ketone proved a more challenging substrate which afforded ester **15** in 51% yield (entry 5). Substituted benzaldehydes also participate in the process—use of 2-naphthaldehyde gave **16** in good yield (entry 6), however the highly hindered mesitaldehyde appears to be beyond the orbit of this methodology and failed to produce **17** under these conditions (entry 7). Smooth coupling was observed in cases involving halobenzaldehydes and trifluoromethylketones within 3 hours reaction time (**18–20**, entries 8–10).

Of particular interest is the coupling of an aliphatic aldehyde (entry 11) with trifluoromethylacetophenone. This reaction is complicated by competing deleterious thiolate-catalysed aldol pathways, however in the presence of a modest excess of the ketone (entry 11), a substantial yield of the coupled product **21** could be isolated. The use of the more enolisable 2-phenylpropanal led to the formation of **22** with reduced product yield as a mixture of diastereomers (entry 12). To the best of our knowledge these represent the first example of such a coupling between these substrate classes.

To summarise, the synthetic utility of the recently developed thiolate-catalysed Tishchenko reaction was potentially limited by poor catalyst turnover frequency, which led to a requirement for long reaction times. As part of a programme aimed at circumventing this problem it was found that the corresponding microwave assisted reactions proceeded with significant rate acceleration—the prototype disproportionation of benzaldehyde proceeded with over 90% yield in 30 min in the presence of half the catalyst loading required to achieve a similar product yield in 48 h using the previously reported thermal procedure.

The more challenging crossed-Tishchenko process was also found to be susceptible to the influence of microwave irradiation. Product yields were marginally lower than those possible using the thermal process; however good–excellent yields of crossed-products were obtainable in 3 h or less across a range of substrates. The microwave-assisted protocol was also utilised to demonstrate the first examples of the intermolecular Tishchenko coupling of aliphatic aldehydes and an activated ketone.

Studies to further improve the scope and utility of these microwave assisted Tishchenko processes are underway in our laboratories.

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17 The reaction does not proceed with appreciable efficiency in alternative solvents such as CH_2Cl_2, MeCN, PhMe or EtOAc.

18 Given its superior microwave radiation conducting properties (relative to THF) we also investigated the use of 1,4-dioxane in microwave-irradiated reactions, without any observable improvement.

19 We would suggest that this is because in the case of the homo-Tishchenko reaction (unlike in the crossed variant) that acyl-transfer is not rate-determining. Therefore the use of a catalyst such as **10** (designed to make the thioester electrophile as reactive as possible at the expense of thiolate nucleophilicity) is not advantageous.