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Straightforward Reductive Esterification of Carbonyl Compounds with Carboxylic Acids through Tosylhydrazone Intermediates

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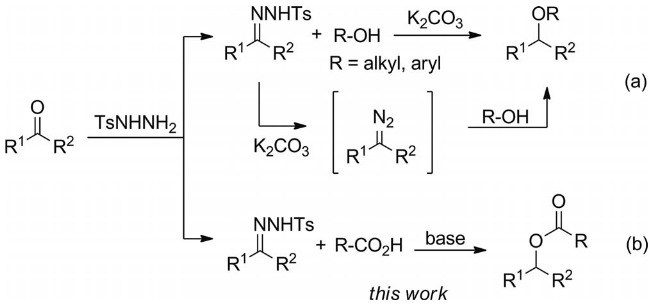
The reaction of carboxylic acids with tosylhydrazones in basic media gives rise to the corresponding esters through an O–H insertion reaction in the in situ generated diazo compound. The process is operationally very simple, catalyst free, and very general with regard to the structure of both coupling partners. In particular, the esterification can be accomplished by employing tosylhydrazones derived from enolizable carbonyl compounds. Considering the ready availability of tosylhydrazones from carbonyl compounds, this reaction can be visualized as a reductive esterification of carbonyl compounds.

Introduction

The development of sustainable chemical reactions is a major challenge in current organic synthesis. In this regard, processes that can be carried out under very simple reactions conditions and in the absence of metal catalysts are highly desirable. Very recently, sulfonylhydrazones have been shown to be very versatile intermediates towards this purpose. In particular, the base-promoted decomposition of sulfonylhydrazones (the Bamford–Stevens reaction)[1] represents a very effective way to carry out the chemistry of diazo compounds starting from carbonyl compounds.[2] This type of chemistry had been generally restricted to hydrazones derived from non-enolizable carbonyls that generate relatively stable diazo compounds.[3] However, in recent years several examples of transition-metal-catalyzed reactions,[4] as well as transition-metal-free processes,[5] have appeared that employ tosylhydrazones derived from enolizable carbonyl compounds, expanding the chemistry of these well-known synthetic intermediates. In particular, we have recently described a new method for the synthesis of ethers by reaction of alcohols and phenols with tosylhydrazones in a very simple process that takes places just in the presence of K_2CO_3 as base (Scheme 1, a).[6,7] The mechanism proposed for this transformation would involve the decomposition of the tosylhydrazone to give a diazo compound that would then undergo the O–H insertion reaction.



Scheme 1. (a) Transition-metal-free reductive etherification of tosylhydrazones. (b) This work.

As a natural extension of this work we decided to investigate a closely related transformation, employing carboxylic acids as the O–H source, in the idea that it might represent a convenient and simple method to carry out the reductive esterification of carbonyl compounds (Scheme 1, b). Indeed, the O–H insertion of carboxylic acids in diazo compounds is well known; however, these reactions seem to be restricted to stabilized diazo compounds or require quite sophisticated synthetic operations to generate the diazo compound.[8] In this paper we wish to report our results in this regard, which have resulted in an operationally very simple and fairly general method for the reductive esterification of carbonyl compounds.

Results and Discussion

In a first approximation, a two-step sequence was studied. Thus, treatment hydrazones **1** in a toluene/0.4 M aqueous NaOH biphasic system, in the presence of a tetra-

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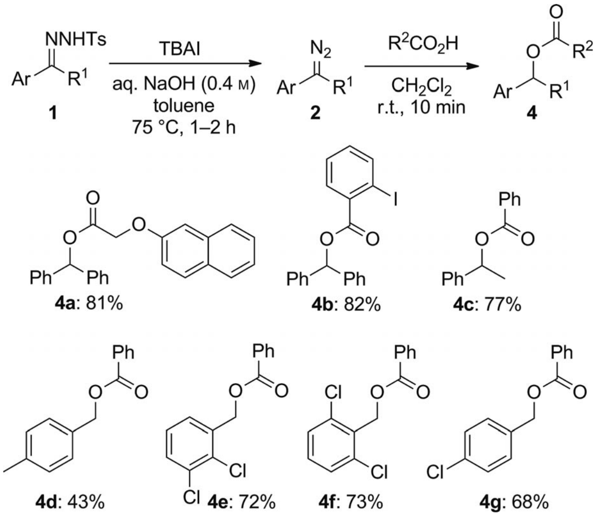
butylammonium iodide phase-transfer catalyst, provided a solution of diazo compound **2** that could be extracted with CH_2Cl_2. Then, addition of carboxylic acid **3** led cleanly to the obtention of corresponding ester **4** (Scheme 2). This straightforward methodology was compatible with tosylhydrazones derived from non-enolizable carbonyl compounds such as benzophenone and aromatic aldehydes. Moreover, the process could be conducted successfully also with the hydrazone of acetophenone. Therefore, this procedure is quite convenient for the protection of carboxylic acids as benzyl or benzhydryl esters.[9]



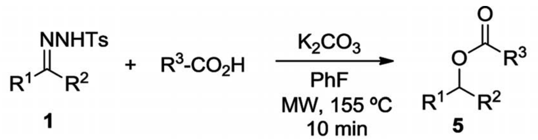
Scheme 2. Reductive esterification of tosylhydrazones through a two-step process.

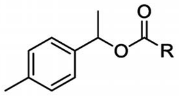
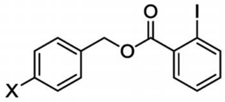
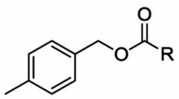
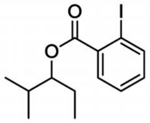
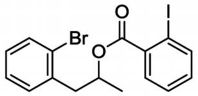
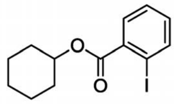
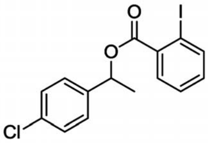
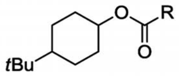
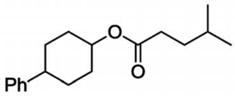
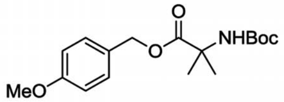
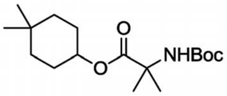
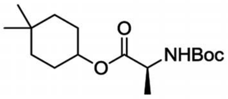
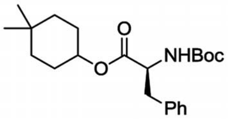
In order to conduct the reaction in a simpler way, avoiding the isolation of the diazo compound, which might enable the esterification of more challenging hydrazones, we decided to apply reaction conditions similar to those previously reported for the reductive etherification of phenols.

For the optimization of the reaction conditions we selected the coupling between *o*-iodobenzoic acid and the tosylhydrazone derived from acetophenone. Following our previous experience with phenols, the initial experiments were conducted under microwave irradiation and by employing K_2CO_3 as the base. As expected, ester **5a** was cleanly obtained as the reaction product. After some experimentation, the best reaction conditions found comprised the employment of a slight excess amount of carboxylic acid **3**, in the presence of 3 equiv. of K_2CO_3 and in fluorobenzene as solvent, at 155 °C for 10 min. These reaction conditions were applied to a collection of tosylhydrazones and carboxylic acids leading to the corresponding esters **5** in yields ranging from moderate to good (Table 1).

Regarding the structure of carboxylic acid **3**, the process can be applied to aromatic and aliphatic carboxylic acids. Bulky *o*-substituents on the aromatic ring are well tolerated (Table 1, Entries 1, 4–7, 13–16). Moreover, α-substituted carboxylic acids also participated in the process successfully (Table 1, Entries 3, 9–12). Additionally, the reaction could be applied for the esterification of amino acid derivatives (Table 1, Entries 20–23).

Table 1. Microwave-promoted reductive esterification of tosylhydrazones with carboxylic acids.[a]



Entry	Compound		Yield [%][b]
1		**5a**: R = 2-IC$_6$H$_4$	52
2		**5b**: R = 1-naph	70
3		**5c**: R = *c*-pent	58
4		**5d**: X = Me	62
5		**5e**: X = MeO	68
6		**5f**: X = F	52
7		**5g**: X = H	55
8		**5h**: R = 1-napth	70
9		**5i**: R = isopentyl	59
10		**5j**: R= *c*Bu	60
11		**5k**: R = *t*Bu	56
12		**5l**: R = adamantyl	59
13		**5m**	59
14		**5n**	40
15		**5o**	60
16		**5p**	70
17		**5q**: R = *t*Bu	58[c]
18		**5r**: R = *c*-Bu	45[c]
19		**5s**	55[c]
20		**5t**	65
21		**5u**	57
22		**5v**	52
23		**5w**	66

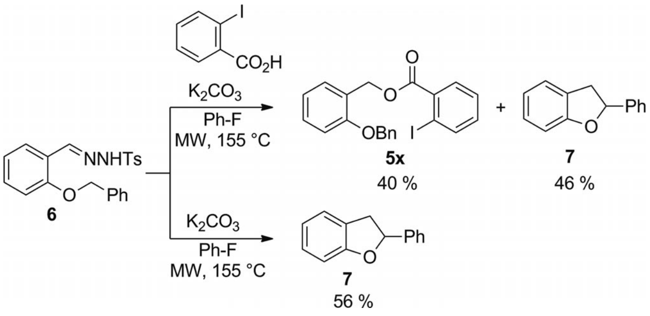
[a] Reaction conditions: Tosylhydrazone **1** (0.5 mmol, 1 equiv.), carboxylic acid **3** (1.2 equiv.), K_2CO_3 (3.5 equiv.), PhF (2.5 mL), MW, 155 °C, 10 min. [b] Isolated yield after column chromatography. [c] Obtained as a 1:1 mixture of diastereoisomers.

Like in the preceding method, the reaction of carboxylic acids with hydrazones derived from aromatic aldehydes proceeded well, giving rise to the corresponding benzyl esters, and therefore, this methodology could be employed as an alternative procedure for the benzylation of carboxylic acids. However, the microwave-promoted reaction failed for the introduction of the benzhydryl group from benzophenone hydrazone. Nevertheless, this type of ester can be formed by employing the stepwise method described above.

Interestingly, the microwave-promoted reaction is compatible with a variety of sulfonylhydrazones, including those derived from enolizable dialkyl ketones, a type of hydrazone that is particularly challenging, because it undergoes very easy decomposition through the diazo compound to give the corresponding alkene. Examples of the employment of cyclic and acyclic dialkyl tosylhydrazones are presented in Table 1 (Entries 13–15, 17–19, 20–22).

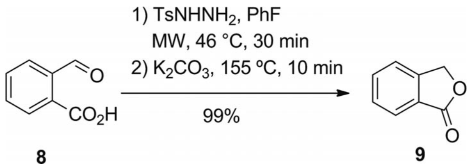
The diastereoselectivity of the reaction was studied by employing hydrazones derived from 4-substituted cyclohexanones (Table 1, Entries 17–19). Unfortunately, no diastereoselectivity was observed, and the esters were obtained as a 1:1 mixture of diastereoisomers.

Noteworthy, the reaction with hydrazone **6**, which features a benzyloxy group in the *ortho* position relative to the hydrazone, gives rise to a mixture of expected benzyl ester **5x** and dihydrobenzofuran **7**. Indeed, in the absence of the carboxylic acid, dihydrobenzofuran **7** was obtained in 56% yield under the same reaction conditions. Formation of compound **7** could be explained by intramolecular insertion of the benzylic C–H bond on the incipient carbene generated from the diazo compound (Scheme 3). This transformation of *o*-benzyloxytosylhydrazones has been previously reported in the presence of a Rh catalyst[10] but not under transition-metal-free-conditions. However, the analogous metal-free version employing *o*-aminobenzaldehyde derivatives leading to indolines has been recently documented.[11] We are currently evaluating the scope of this transition-metal-free heterocyclization as a new entry to the benzofuran scaffold, and the results will be reported in due course.



Scheme 3. A C–H insertion reaction of *o*-benzyloxytosylhydrazones.

Finally, preliminary experiments of lactonization have been conducted. In this case, the reaction was carried out in a one-pot fashion from the carbonyl without isolation of the intermediate hydrazide. Thus, treatment of 2-formylbenzoic acid **8** with tosylhydrazide in PhF, followed by addition of K_2CO_3 and MW irradiation led to the obtention of phthalide **9** in quantitative yield (Scheme 4). We are currently evaluating the scope of this methodology.



Scheme 4. A one-pot reductive lactonization of an oxoacid.

Conclusions

We have reported a new esterification methodology by reaction of carboxylic acids with tosylhydrazones that occurs through the insertion of O–H into diazo compounds generated in situ from tosylhydrazones. The methodology exhibits wide scope with regard to the structure of the hydrazone, including those derived from enolizable ketones. Moreover, the reactions proceed without the need of a catalyst and are operationally very simple, safe, and fast. From a synthetic point of view, the process can be envisioned as a reductive esterification of carbonyl compounds promoted by tosylhydrazide.

Experimental Section

Stepwise Esterification: A solution of the appropriate tosylhydrazone (0.5 mmol) in toluene (10 mL) was added to a stirred mixture of tetrabutylammonium iodide (0.018 g, 0.05 mmol) in 0.4 м KOH (1.25 mL, 0.5 mmol). The reaction mixture was heated at 75 °C for 1–2 h. The reaction mixture was cooled to room temperature and the characteristic colored organic layer was separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL). The organic phases were combined, and the corresponding carboxylic acid (0.5 mmol) was added. Nitrogen evolution occurred, and the resulting mixture was stirred for 10 min at room temperature. The mixture was dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the final product was purified by column chromatography (SiO_2; hexane/AcOEt, 95:5).

Reactions Performed Under Microwave Irradiation: A 2–5-mL microwave vial was charged with potassium carbonate (241.5 mg, 3.5 equiv.), tosylhydrazone 1 (0.5 mmol), PhF (2.5 mL), the carboxylic acid (0.3 mmol, 0.6 equiv.), and a magnetic stirring bar. The vessel was sealed with a septum, placed into the microwave cavity, and irradiated to heat the reaction mixture at the desired temperature in a Biotage Initiator microwave apparatus. The total heating time was 10 min at 155 °C. When the reaction was complete, the vial was cooled down to room temperature by using a propelled air flow. It was then opened and poured into a separatory funnel. The layers were separated, and the aqueous phase was extracted (3 × 10 mL) with dichloromethane. The combined organic layers were washed with brine, dried with Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the final product was purified by column chromatography (SiO_2; hexane/AcOEt, 95:5).

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra for all final products.

Acknowledgments

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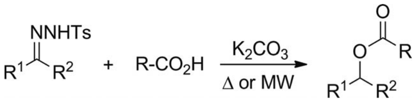
Reductive Esterification

Esters can be readily obtained by reaction between the tosylhydrazones of aldehydes or ketones and carboxylic acids through an operationally very simple procedure that requires only the presence of K_2CO_3 as base.



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