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A simple and efficient transprotection of aryl methyl ether to aryl benzoate under microwave activation

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Abstract—A simple and efficient method for the transprotection of aryl methyl ether to easily cleavable arylbenzoate mediated by microwave activation has been developed. One important feature of this method is its high tolerance towards sensitive functionalities and to some extent to bulky environment.

Despite the tremendous efforts and achievement in the development of highly selective reaction, organic synthesis is still relying on the extensive use of protecting groups. The development of new selective methodologies for the protection and deprotection of sensitive functionalities is therefore an ongoing task.[1] Although slightly less developed, transprotections are appearing as highly valuable tools in synthesis since by combining deprotection and protection in a single step they offer a 'do one, get one free' method to the synthetic chemist. Besides the well-known and useful transformation of enol ether to ketals,[2] some transprotections have appeared for the interconversion of allylcarbamates to amides or dipeptide,[3] thioester to thioether or thioketal,[4] silyl ether to benzyl ether or ester,[5] enol ether to thioketals[6] and silyl ethers to acetates of nucleosidic structures.[7]

Regarding the phenol group, both its acidity and low redox potential make its protection compulsory. It is also noteworthy that typical harsh reaction conditions used in aromatic core chemistry require the use of highly stable protecting groups. Consequently the deprotection of the latter cannot be performed once the phenoxy core is surrounded by more sensitive functionalities. Typically, alkyl aryl ethers exhibit a very high stability naturally meaning that their cleavage suffers drastic conditions making the latter highly substrate dependant.[8] It is therefore of importance to perform an interconversion from a highly stable protecting group to a more labile one under virtually neutral conditions. An interconversion of an aryl isopropyl ether to an aryl acetate by a TMSOTf activation has been recently reported.[9] Moving from isopropyl to methyl would be advantageous not only from the point of view of atom economy but also because of the wide availability of aryl methyl ether. Although numerous methods have been reported for the deprotection of aryl methyl ether,[10] to our knowledge, only one patent has described its transprotection to an aryl ester.[11] This has been carried out using a substoichiometric amount of guanidinium disalt such as **1** (Fig. 1).

The transformation under thermal conditions was efficient on model substrates such as anisonitrile **2** but required high temperature for a long reaction time (24 h at 180 °C). This prompted us to explore the development of this uncommon reaction under microwave activation. Indeed, the use of microwave, by allowing significant rate enhancements of well-known reactions,

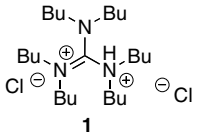

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Figure 1. Hexabutylguanidinium chloride hydrochloride.

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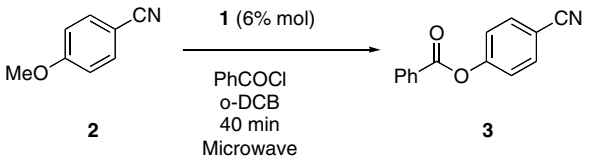
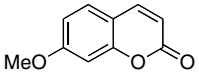
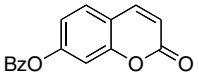
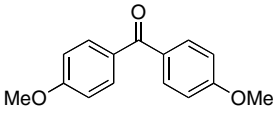
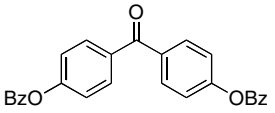
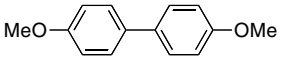
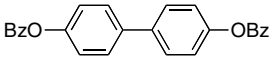
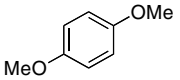
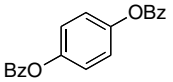
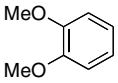
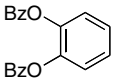
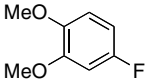
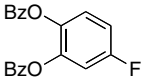
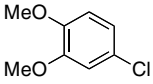
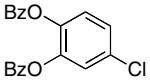
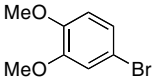
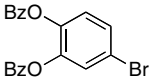
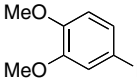
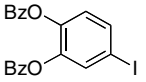
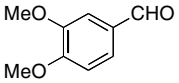
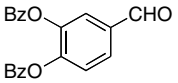
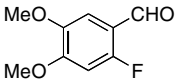
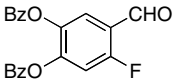
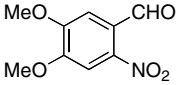
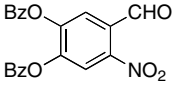


Scheme 1.

has allowed important achievements in organic chemistry.[12] It has been nicely applied especially in heterocyclic chemistry,[13] as well as in deprotection of aryl methyl ethers.[14] We are here reporting the first application of microwave activation to the transprotection of aryl methyl ethers. Applied on an array of aryl methyl ethers, the corresponding aryl benzoates have been accessed, providing a new and fast alternate process carried out under neutral conditions.

In the case of this transprotection, we suspected that both the ionic character of the catalyst and the strong dipolar momentum of the solvent (*o*-dichlorobenzene) would allow the reaction to benefit of a significant microwave activation.[15] Our expectations were confirmed, the reaction being significantly accelerated. Indeed after 40 min, 4-cyanophenyl benzoate **3** was isolated in 99% yield after a simple precipitation in pentane (Scheme 1).[16,17]

Table 1. Transprotection of aryl methyl ethers to aryl benzoate

Entry	Starting material	Product	Reaction time (min)	Isolated yield[a] (%)
1			40	75
2			40	92[b]
3			90	69
4			40	78[b]
5			50	100[b]
6			40	56[b]
7			50	52[b]
8			50	79[b]
9			85	60[b]
10			40	69[b]
11			90	83[c]
12			15	61

[a] Isolated yield after precipitation from pentane.
[b] Similar yields were obtained when the reaction was conducted under solventless conditions.
[c] Similar yields are achieved at atmospheric pressure or in closed vessel.

The scope of this reaction to more functionalized compounds has been explored taking into account both the yield and the reaction time (Table 1). One important aim of this study was to establish a strategy allowing the isolation of the desired product in the most time efficient fashion. This has been achieved by a filtration–precipitation process that allows the isolation of a pure product in less than 30 min leading to an 'overall production time' (reaction + purification) below 2 h.

The coumarin moiety proved stable under these reaction conditions yielding 75% of the benzoylated product in 40 min (entry 1). This reaction was found especially efficient when applied to polymethoxylated compounds. The double transprotection was actually successfully carried out on 4,4′-dimethoxybenzophenone moiety also in 40 min (entry 2). In this case, the presence of an electron withdrawing group such as the ketone seemed to enhance both the reaction rate and the overall efficiency.

Accordingly 4,4′-dimethoxybiphenyl required a reaction time of 90 min (entry 3). Oppositely, on monocyclic systems, the reaction yields seemed to be neither affected by the presence of an electron donating group on the aromatic ring (entry 4) nor by some steric bulk around the ether (entry 5); the reaction times being almost equivalent (40 and 50 min). It must be here pointed out that the two transprotections on *o*-dimethoxyaryls are probably not simultaneous. Therefore the second one is carried out *ortho* to a significantly more bulky benzoyloxy group. Introducing a halogen on the aromatic ring induced variation in terms of reaction rate, the latter increasing with the mesomer donating ability of the halogen. Nevertheless in the four cases, the overall efficiency and reaction rate remain high considering that four reactions are carried out in a single step (entries 6–9). We were pleased to note that sensitive benzaldehydes tolerate well the reaction conditions as seen from entry 10. Interestingly no halogen exchange resulting from an S_NAr process was observed starting from 6-fluoroveratraldehyde (entry 11). Finally a strong deactivation of the aromatic ring by a nitro group was shown highly beneficial, the reaction time being lowered to 15 min (entry 12). It should be noted that in all these cases the average yield for each step of the global reaction is above 85%, which compares well with the standard efficiency of common protection and cleavage reactions. Moreover the reaction time has always been below 90 min, an obviously important feature for reaction carried out at high temperatures.

In conclusion, we have established a new reactivity of aryl methyl ether under microwave activation leading to a very useful and fast transprotection of the phenol moiety. This reaction proved to be equally efficient on polymethoxyaryl. In this latter case only transprotection has been observed; even in the presence of highly activated aromatic rings, no Friedel–Crafts benzoylation is observed. The transprotected product was the only one observed and isolated. Mechanistic studies and developments of this methodology are currently under investigations.

Acknowledgements

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16. Reactions have been performed on a Discover® from CEM Corporation with continuous stirring using the 'Powermax' Function.
17. Representative procedure for preparation of 4-cyanophenyl benzoate **3**: A solution of 4-anisonitrile **2** (4.29 mmol), hexabutylguanidinium chloride hydrochloride **1** (0.26 mmol) and benzoyl chloride (6.44 mmol) in *o*-dichlorobenzene (1 mL) was irradiated at 180 °C (20 W) for 40 min. The reaction mixture was diluted with dichloromethane filtrated over a plug of silica gel and concentrated with a rotary evaporator. Precipitation upon addition of pentane (5 mL) gave 945 mg of **3** (99%).