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Fast deprotection of phenoxy benzyl ethers in transfer hydrogenation assisted by microwave

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Abstract—Phenoxy benzyl ethers are easily and quickly deprotected in the presence of ammonium formate and microencapsulated Pd(0)EnCat with the assistance of microwave irradiation. This procedure can be applied in the presence of other functional groups as well. The described protocol is particularly convenient for the preparation in a parallel and automatic fashion of libraries of compounds possessing a phenol type moiety.

The development of protecting groups and the consequent deprotection is a field of still increasing interest to successfully address more and more complex molecules. Among the protecting groups, the benzyl (Bn) is of widespread use in masking functional groups such as alcohols, phenols, acids and amines.[1,2] In medicinal chemistry the benzyloxy groups are often the precursors of phenols which are present as essential pharmacophore in many well known classes of compounds endowed with pharmacological activity, such as catecholamines, DOPA, β-adrenergics and serotonine derivatives.[3] Although well spanned methods to accomplish the deprotection of phenoxy benzyl ethers do exist, an affordable, clean and fast procedure amenable to automation would be valuable in the preparation of libraries of compounds possessing a free hydroxy function of phenol type. Microwave (MW) assisted organic synthesis is now a well established technique and almost all chemical transformations can be carried out efficiently and in extremely shortened times.[4,5] Only a few microwaves enhanced hydrogenations are reported as gaseous hydrogen is not much compatible with MW technique mainly for safety reasons. To overcome these drawbacks dedicated reactors have been recently developed[6] or, as a preferred option, hydrogen donors such as formate salts, cyclohexene and analogues are used[7,8] according to transfer hydrogenation conditions. The debenzylation processes both under traditional conditions and with microwave assistance are carried out in the presence of Pd/C as a catalyst and this causes some trouble when used in the automated preparation of libraries. First, a safe handling is hampered by its pyrophoric nature. Second, nano particles of palladium, in many cases not compatible with biological screening, still remain into the crude product after filtration.

We report here a new method for the O-debenzylation of phenoxy compounds well suited for the rapid preparation of substances for pharmacological screening. To the best of our knowledge O-debenzylation in transfer hydrogenation assisted by microwaves has been reported only for aliphatic alcohols.[9] We now expand the scope of the process to aromatic substrates of phenol type and along with the MW assistance accomplished in a sequential automated fashion we introduce the use of microencapsulated Pd(0)EnCat™ as a catalyst which couples a safe and easy handling with a decreased product contamination (less than 10 ppm) caused by metal leaching.[10–13]

To explore fast and set up a suitable method as a model compound we selected 1-(4-benzyloxyphenyl)-piperazine, hydrochloride (**1**). It contains the target benzyl ether, it has an amine function which allows for a rapid detection in LC/MS of the formed compounds, it has a chromophore well suited for detection and quantisation

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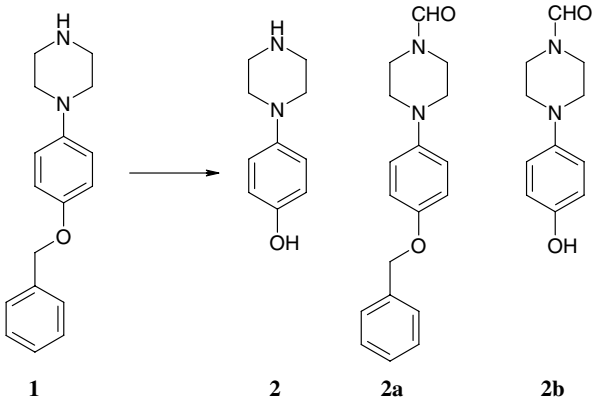
under UV light at 254 nm. Moreover, its core structure has a 'drug like' pattern which is well present in a lot of pharmacologically active compounds. Initial debenzylation experiments were carried out for comparison purposes in a conventional manner using ammonium formate as a hydrogen source and *n*-butanol as a solvent in the presence of 10% Pd/C or Pd(0)EnCat™ NP30. In the former case, complete deprotection was achieved after 4 h at 90 °C, whereas in the latter under the same temperature and time parameters the conversion was 80%. This confirmed that an incapsulated catalyst under transfer hydrogenation conditions could serve in the O-debenzylation process.

To find out the best conditions a 48 reaction matrix was designed to consider up to five parameters: (a) temperature at 80, 100 and 120 °C; (b) solvents 1,3-propandiol and DMF (300 μl) to ensure good MW efficiency owing to a high tan δ value and proper swelling of the resin on which the catalyst is immobilised; (c) reaction times of 5 and 10 min; (d) catalyst in 7% and 14% amount; (e) ammonium formate added in 5 and 10 equuiv amount. The matrix was divided in two sets, each embracing 24 reactions carried out on a 45 mg (0.15 mmol) scale (being the catalyst at 7% in the first set and at 14% in the second set) based on the capacity of the automated carousel of the instrument CEM (Explorer model), and submitted to microwave irradiation. Scheme 1 shows all the compounds identified in the debenzylation reaction. Along with the expected 4-hydroxy-phenyl-piperazine (**2**) the formyl derivatives of both the starting material (**2a**) and the target compound (**2b**) were detected in different amounts according to the different conditions exploited.



Scheme 1. Debenzylation of the model compound.

The results from the matrix, expressed as % of conversion into the expected compound **2** as detected by automated LC/MS at 254 nm (λ) in a graphic 3D format (Fig. 1), make clear the effects of the investigated parameters. (a) Temperature: the optimal is 80 °C as its increment to 100 °C decreases the conversion with by-products **2a** and **2b** present in a high amount. At 120 °C, there is a marked effect on the resin: it decomposes with the consequent release of the encapsulated catalyst along with several resin related impurities which hamper any reaction evaluation. The temperature limits were also confirmed in trials without the probe compound and the ammonium formate. (b) Solvent: DMF appears clearly superior to 1,3-propandiol. As an explanation it can be put forward that the parameters influencing the swelling properties of the Pd(0)EnCat™ resin (120 for DMF vs only 20–30 for 1,3-propandiol)

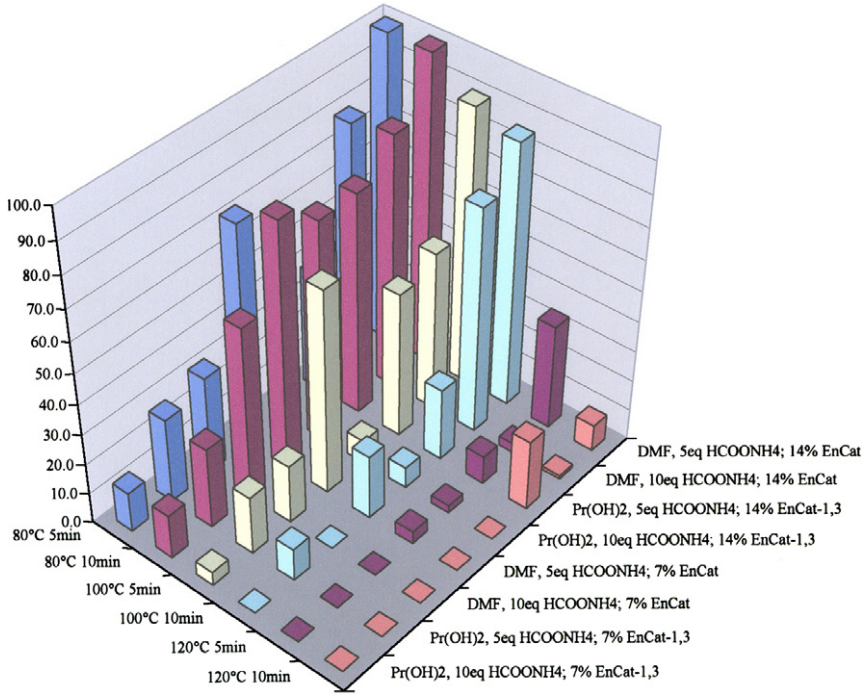


Figure 1. Matrix of the experimental conditions.

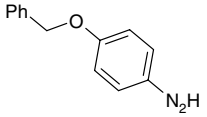
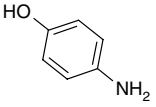
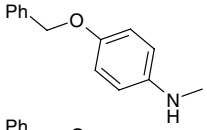
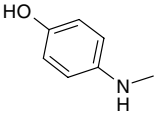
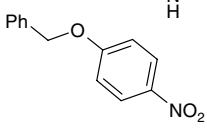
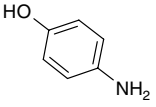
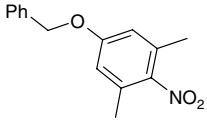
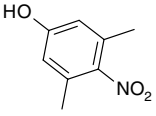
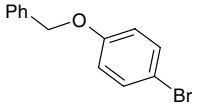
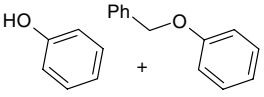
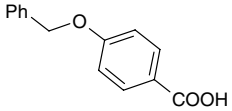
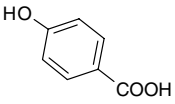
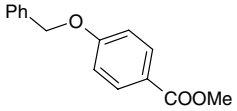
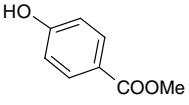
overcome the tan δ values (0.98 vs 0.16 for 1,3-propandiole and DMF, respectively). DMF has an additional favourable effect on the pressure which is increased up to 30–40 psi in comparison to 20 psi in the vials containing 1,3-propandiol. This is due to a higher amount of free hydrogen available and suggests for a better efficiency of DMF in the decomposition of ammonium formate. (c) Reaction time: even if the matrix seems to point slightly in favour of 10 min versus 5 min no substantial difference does exist indeed: it can be concluded that the parameter time is not a key one. (d) Catalyst: a higher percentage (14%) makes always more efficient the process, probably acting on the O-debenzylation itself rather than on the hydrogen transfer step. (e) Ammonium formate: the overall effect is not so remarkable on the conversion (5 equiv are enough to convert almost completely the starting material). Its increase up to 10 equiv results mainly in the increase of the formylated by-products (particularly **2b**).

Based on the tested conditions the optimised parameters for the O-debenzylation reactions have been defined as follows: the compound (0.15 mmol) dissolved in DMF (300 μl) is reacted at 80 °C for 10 min under microwave conditions in the presence of 14% of Pd(0)EnCat™ and 5 equiv of ammonium formate.[14] According to the defined experimental protocol the reaction in the case of model compound (**1**) has been successfully scaled from the initial 45 mg (0.15 mmol) up to 1 g (3.33 mmol) using in this case a 80 ml vial and getting the same results. This shows that the present procedure is of use not only in the preparation of a small amount of test compounds but in the preparation of intermediates as well.

In a further step, the present defined best conditions have been applied to other substrates to evaluate the scope and the limitations of this new method for the fast deprotection of O-benzyl groups of aromatic type. To this end other O-benzylated phenyl and heterocyclic rings bearing the benzyloxy functionality alone or in the presence of other representative and common functional groups have been selected and submitted to MW irradiation under the established conditions. In Table 1 are collected both the substances investigated along with the results obtained in terms of the percentage of conversion into the expected compound and of the structure and the yield of the compound actually isolated.

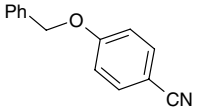
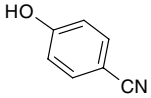
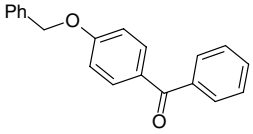
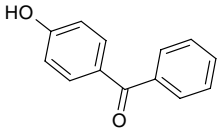
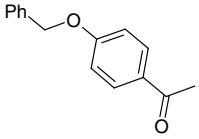
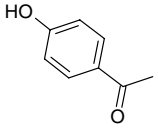
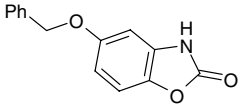
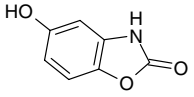
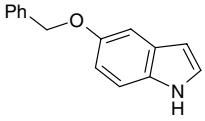
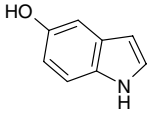
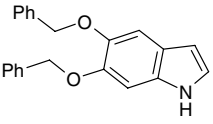
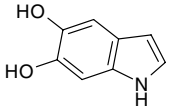
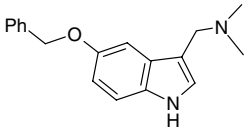
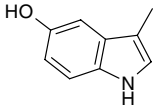
Functional groups such as carboxylic acid, methyl ester, cyano and carbonyl (ketone type) survive pretty well to

Table 1. Examples of O-debenzylation with ammonium formiate and Pd(0)Encat under MW

Entry	Substrate	Conversion[a] (%)	Product[b]	Yield[c] (%)
a		60		50
b		52		45[d]
c		0		20
d		35		27[e]
e		0		0
f		100		93
g		100		95

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Conversion[a] (%)	Product[b]	Yield[c] (%)
h		100		92
i		92		85
j		100		85
k		96		89
l		95		90
m		100		95
n		0		92[f]

[a] % of the expected compound as determined in the crude reaction mixture by LC or GC/MS.
[b] All compounds, unless differently specified, were identified in comparison with authentic commercially available samples.
[c] Isolated yield.
[d] Spectroscopic data and mp (85–87 °C) in agreement with the literature.[15]
[e] Spectroscopic data and mp (104 °C) in agreement with the literature.[16]
[f] Spectroscopic data and mp (109–110 °C) in agreement with the literature.[17]

the debenzylation conditions and the expected compounds can be isolated in very high yields (entries **f**–**i** and **j**). The primary and secondary amino groups (entries **a** and **b**, respectively) suffer from a simultaneous formylation reaction. The formation of the related by-products accounts for the observed low conversion percentage and for the low yield of the actually isolated compound. The nitro and the halogen groups do not survive to the present process as they are preferentially reduced with respect to the benzyl group (entries **c** and **e**). In the crude reaction mixture never were detected the substances deriving from the single debenzylation step, as indicated by LC/MS or GC/MS analysis. In a particular case (entry **d**) the O-debenzylated compound still with the preserved nitro group was observed and isolated albeit in a rather low yield. This effect was ascribed to the presence of two methyl groups in *ortho*-position which in some way shield the nitro negatively affecting its reaction rate. The present process can be also successfully applied to heterocyclic structures. Both benzo-oxazolone and indole cores are readily and efficiently debenzylated (entries **k** and **l**). Also the presence of two benzyl groups can be handled quite similarly with good results (entry **m**). The last example refers to 5-benzyloxy-3-dimethylaminomethyl indole: here the dimethylamino methyl groupment could not be preserved and 3-methyl-5-hydroxy indole was obtained in a good yield. It can be argued that the indole core looks like a *N*-benzyl moiety with respect to the dimethyl amino function and consequently this portion under the applied conditions is readily debenzylated as well.

With the present investigation we provide a new, fast method for the O-debenzylation of aromatic substrates in transfer hydrogenation which takes advantage of new technologies such as microwave irradiation and microencapsulated catalysts. This bunch of techniques coupled with automation provided by new MW reactors are of particular value in the preparation of libraries of compounds of potential pharmacological interest.

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14. *Typical procedure for O-debenzylation reaction in an Explorer CEM microwave reactor (10 ml vial)*: 0.15 mmol of the compound (**1** or the entries **a**–**n** in Table 1) was dissolved in DMF (300 μl). Ammonium formate (47 mg, 5 equiv) and Pd(0)EnCat™ (54 mg, 14 equiv) were added and submitted to microwave irradiation for 10 min (80 °C, 5 min ramp, potency 30–40 W, stirring on, cooling on). The reaction mixture was diluted with MeOH (600 μl) and filtered. An aliquot was submitted to LC/MS or GC/MS analysis and the remaining solution evaporated to dryness in a speed-vac. The compounds were isolated with traditional methods such as crystallisation, elution on SCX cartridges or mass driven LC purification. The isolated compounds were identified by comparison on NMR and LC/MS or GC/MS with authentic samples in case of commercially available compounds and with spectroscopic data and m.p. in agreement with those reported in the literature in the other cases.
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