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COMMUNICATION

Highly efficient chemoselective *N*-TBS protection of anilines under exceptional mild conditions in the eco-friendly solvent 2-methyltetrahydrofuran†

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A straightforward chemoselective protection of anilines as *N*-TBS derivatives is described by using a suitable deprotonation of the amine with methyllithium in the environmentally friendly and safer substitute of THF, 2-methyltetrahydrofuran, under exceptional mild reaction conditions (0 °C, 30 min). Interestingly, the protecting group maybe cleaved efficiently by simple treatment of *N*-TBS-anilines with silica gel in ethanol–water.

The use of protecting groups (PGs) in organic synthesis is a widely known procedure that allows modulation of the chemical reactivity of those functional groups which may react in an undesired manner or lead to the destruction of the compound.[1] It is evident that the use of PGs lengthens a synthesis by at least two steps (protection/deprotection) with the inevitable reduction in yield, in atom-economy and increase in cost;[2] in this sense, the 8th Principle of Green Chemistry[3] clearly states that these protective steps should be minimized or avoided, but in those cases in which protection is mandatory, it is absolutely necessary to develop highly efficient protocols.

In this context, the protection of amino groups is an interesting research field, because of its well-established use during the preparation of many different structures possessing biological activity.[4,5] In this regard, *N*-silylamines[6] are widely-used protecting groups because of the absolutely mild conditions required for their removal[2] (acidic treatment, TBAF), and thus they may be viewed as ideal amine-protecting groups, when increasing the nucleophilicity of the nitrogen is the desired target. However, despite this advantage compared to *N*-alkyl groups (demanding harsh conditions for their removal,[1] such as hydrogenolysis, photolysis, metal reduction or transition metal isomerization), their high sensitivity towards moisture and hydrolytic conditions severely limits their employment in synthesis:[2] for example, *N*-TMS protected anilines (useful materials for the Pd-catalyzed aryl amination in $scCO_2$[7,8] or for the synthesis of *O*-silylcarbamates and ureas in $scCO_2$)[9] must be mandatorily stored under nitrogen at –20 °C to prevent their degradation; in addition, solvents in which reactions are performed should be removed *via* distillation under nitrogen. Furthermore, their preparation both by amine deprotonation with *n*-BuLi at –78 °C[7,8] or by an organic base (triethylamine,[7–9] DBU[10]) requires long reaction times (17–48 h) to render only moderate yields.

In view of these well-documented difficulties involving the use of TMS anilines, the use of *tert*-butyldimethylsilyl (TBS) analogues has gained widespread attention, because these compounds possess greater stability under different operational conditions, including the presence of organometallics.[2] Anyhow, the synthesis of *N*-TBS structures, under analogous conditions (silylation with TBDMSCl in benzene,[11] or its activated form TBDMS trichloroacetate in 18-crown-6[12]), is not safe from an environmental perspective, due to the high toxicity of the solvents required for such functionalization, that without any doubt constitutes a limitation for their application to the production of fine chemicals (*e.g.* drugs).[13] Similarly, the use of other approaches, such as the transition-metal catalyzed reduction of azo compounds (TBDMSCl-Li-$FeCl_3$) is not always effective, because of the possible concomitant ring silylation that may take place.[14] Alternatively, a Pd dehydrogenative silylation in refluxing toluene has also been employed;[15] however, such technique involves the use of expensive and toxic Pd catalyst and requires long reaction times to reach completion, which is against the 3rd, 4th and 5th Principles of Green Chemistry.[3] In summary, these protocols are not suitable for green processes because of the use of toxic solvents and expensive catalytic systems, and even worse leading to only moderate yields of the desired TBS-anilines.

Due to our interest in developing sustainable methodologies for the functionalization of carbon and heteroatoms,[16–20] we recently described a protocol for the regio- and chemoselective alkylation of imidic-type nitrogen atoms[21] in the eco-friendly solvent 2-MeTHF.[22] This solvent is being increasingly used for replacing THF in different kind of reactions, ranging from

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Table 1 Optimization of the reaction under different conditions. Stoichiometric ratio: aniline (1.0 equiv.)/base (1.05 equiv.)/TBDMSCl (1.05 equiv.)

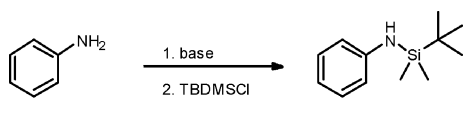
Entry	Base	Solvent	Temperature[a] [°C]	Reaction time [h]	Isolated yield [%]
1	MeLi	THF	–78 °*C*	3	81
2	MeLi	THF	–50 °*C*	2	86
3	MeLi	THF	–20 °*C*	2	83
4	MeLi	THF	0 °*C*	1	75
5	MeLi	Et_2O	–78 °*C*	4	78
6	MeLi	Et_2O	–50 °*C*	3	82
7	MeLi	Et_2O	–20 °*C*	2	76
8	MeLi	Et_2O	0 °*C*	2	66
9	MeLi	MeTHF	–78 °*C*	3	85
10	MeLi	MeTHF	–50 °*C*	2	89
11	MeLi	MeTHF	–20 °*C*	1	94
12	MeLi	MeTHF	0 °*C*	0.5	100
13	MeLi	Toluene	–20 °*C*	6	63
14	MeLi	Toluene	0 °*C*	4	69
15	*n*-BuLi	THF	–20 °*C*	2	80
16	*n*-BuLi	THF	0 °*C*	1	75
17	*n*-BuLi	Et_2O	–20 °*C*	2	71
18	*n*-BuLi	Et_2O	0 °*C*	1	62
19	*n*-BuLi	MeTHF	–20 °*C*	1	86
20	*n*-BuLi	MeTHF	0 °*C*	0.5	91
21	*s*-BuLi	MeTHF	–20 °*C*	1.5	80
22	*s*-BuLi	MeTHF	0 °*C*	2	83
23	*s*-BuLi	THF	–50 °*C*	3	72
24	*s*-BuLi	THF	–20 °*C*	2	66
25	*s*-BuLi	Et_2O	–20 °*C*	3	61
26	*t*-BuLi	THF	–50 °*C*	5	65
27	*t*-BuLi	THF	–20 °*C*	3	61
28	*t*-BuLi	MeTHF	–20 °*C*	2	68
29	MeMgBr	MeTHF	0 °*C*	3	72
30	DBU	MeTHF	25 °*C*	3	65
31	K_2CO_3	MeTHF	25 °*C*	3	56

[a] Referred to the addition of the base to the amine then, after the trapping with TBDMSCl temperature was allowed to reach rt.

organometallics[23–27] to organocatalysis[28,29] or biocatalysis.[30–32] Moreover, we have used it as a suitable solvent for the highly 1,2-regioselective addition of organolithiums to α,β-unsaturated carbonyl-like compounds, thus evidencing a series of advantages over usual ethereal solvents, especially the ability to carry out such additions under mild conditions.[33]

This ethereal solvent possesses a series of chemical characteristics that justify its employment as a good alternative of THF:[22] (a) its low solubility in water (14 g/100 g, at 20 °C) does not require the addition of solvents (mainly diethyl ether or aromatic hydrocarbons) during the reaction work-up, so that extraction of reaction products is improved; (b) since it forms an azeotrope with water, the drying procedure of this solvent is effectively achieved by a simple distillation, avoiding the use of the Na/benzophenone technique used for THF; (c) it presents a constitutional higher stability[34] compared to THF to undergo degradation processes in the presence of organolithiums that by abstracting a proton from THF may initiate fragmentations[35] *via* reverse cycloaddition [3 + 2] (the so-called α-cleavage) with obtainment of ethylene and the lithium enolate of acetaldehyde. On the other hand, in the case of 2-MeTHF a significant decrease of the α-cleavage was observed in the presence of organolithiums ($t_{1/2}$ = 130 min for 2-MeTHF *vs.* $t_{1/2}$ = 10 min for THF).[34] In addition, its environmental and safety features contribute to improve its profile compared to THF: (a) since its precursor (furfural) proceeds from renewable sources (waste biomass) CO_2 emissions are eliminated and thus the 7th principle of Green Chemistry is satisfied;[3] (b) its high boiling point (80.2 °C) decreases the amount of solvent released in the air; and (c) as established very recently by scientists at Merck in a toxicological study,[36] the exposure to this solvent is not associated with genotoxicity and mutagenicity, thus supporting its employment in the preparation of fine chemicals. Unfortunately, the well-known peroxide formation in the absence of stabilizers inherent to the use of THF is also observed when using 2-MeTHF.[22]

In this work, we show a suitable protocol for the *N*-TBS protection of aniline derivatives based on the deprotonation to afford the corresponding lithium amide and subsequent trapping with TBDMSCl. (Scheme 1)



Scheme 1 *N*-TBS protection of aniline.

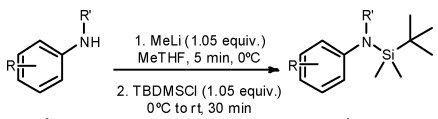
The results of such a transformation under different conditions are shown in Table 1: as can be seen, those reactions performed with organolithium compounds (entries 1–28) give the highest yields compared to organomagnesium (entry 29) or no-organometallic conditions (entries 30–31). Among the series of organolithium compounds, regardless the solvent employed, methyllithium affords the best results (entries 1–14) compared to

secondary (entries 21–25) or tertiary alkyl reagents (entries 26–28), probably because its lower steric hindrance does not affect the proton abstraction.

The effect of the solvent is remarkable, and its correct choice establishes the optimization of the reaction: thus, apolar aprotic solvents afforded lower yields and contemporaneously increased reaction times (entries 13–14). On the contrary, polar aprotic ones led to higher yields in shorter reaction times, MeTHF being the best solvent for such transformation (entries 9–12, 19–22, 28). The key role played by the solvent on the course of the reaction is reaffirmed taking into account that the use of both diethyl ether and THF allowed good yields (although not comparable with those achieved with MeTHF), only when temperature was kept below −50 °C during the addition of MeLi (entries 1–2, 5–6, 23, 26). On the other hand, by increasing temperature above −50 °C in diethyl ether and THF (entries 3–4, 7–8, 15–18, 24–25, 27), the yields were significantly lower, and some unidentified impurities in crude reaction were detected by ^{1}H-NMR. Much to our surprise, the use of MeTHF allowed a successful *N*-TBS protection to be performed under the mildest reaction conditions (0 °C, 30 min), thus obtaining the desired product **2** in quantitative yield (entry 12) without needing further purification (only a filtration on a short pad of Celite[37] was effected to remove LiCl formed during the reaction). This peculiarity of MeTHF can be explained on the basis of its aforementioned higher stability in strongly basic media compared to other ethers.

These impressive results prompted us to extend this effective protocol to substituted anilines: in fact, as shown in Table 2, those reactions performed under the optimized reaction conditions afforded exclusively the *N*-TBS adducts in excellent results, without the necessity of purification after the work-up. As can be seen, no difference was observed switching from electron-releasing substituted anilines (entries 1–3, 7) to electron-withdrawing ones (entries 4–6, 8–12); presumably, as a consequence of the rapid and complete deprotonation of the amines to render the corresponding lithium amides, the nucleophilic substitution on the Si atom of TBDMSCl occurs so rapidly that the intrinsic different features relative to anilines bearing substituents with opposite electronic effect may not be invoked for such transformations. Similarly, steric hindrance on the nitrogen atom did not affect its efficient protection, as noted by the easy introduction of the TBS group in secondary amines (both alkyl and alkylaryl, entries 13–15). In this context, it should be emphasized that the superior performance of this protection protocol compared to the previous one (involving the reduction of not readily available azo compounds by Li metal), which in the case of compound **4n** afforded only a modest 72% yield.[14]

Table 2 *N*-TBS protection of different substituted anilines

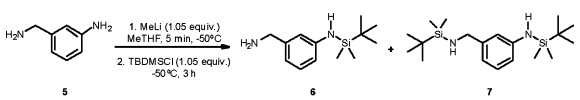


3a-p 4a-p

Entry	R	R′	Isolated yield [%]
1	2,3-dimethyl	H	**4a** (95)
2	3,5-dimethoxy	H	**4b** (97)
3	3-methoxy	H	**4c** (95)
4	3,4-difluoro	H	**4d** (91)
5	3-trifluoromethyl	H	**4e** (98)
6	4-nitro	H	**4f** (94)
7	3-fluoro-4-morpholino	H	**4g** (90)
8	2-iodo	H	**4h** (97)
9	4-bromo	H	**4j** (98)
10	4-acetyl	H	**4k** (90)
11	4-ethoxycarbonyl	H	**4l** (93)
12	4-cyano	H	**4m** (98)
13	H	methyl	**4n** (91)
14	H	benzyl	**4o** (88)
15	H	phenyl	**4p** (93)

It is worth noting the effectiveness of the protocol in the cases of anilines bearing a substituent that could *per se* react with a powerful organolithium compound: thus, it should be highlighted that no lithium/halogen exchange takes place at 0 °C for sensitive iodo- and bromoanilines (entries 8–9) by using MeTHF as the solvent: in contrast, this reaction was reported for 4-bromoaniline at 0 °C with *n*-BuLi in diethyl ether,[38] as a consequence of the transmetallation. Analogously, no traces of any *ortho*-lithiation were observed in the case of fluoroanilines (entries 4, 7) as observed by treating them in THF at −78 °C.[39] These two examples clearly show the importance of the choice of the solvent in order to achieve a highly chemoselective procedure. Moreover, it was also possible to protect anilines in which electrophilic moieties (nitrile, ester, ketone) were constitutively present (entries 10–12), which could suffer the attack of methyllithium: in no case this undesired process was observed, so therefore we can conclude that *N*-TBS aniline protection performed in 2-MeTHF is perfectly applicable to a range of aromatic amines widely substituted, in much milder reaction conditions (0 °C) than those previously described.

Finally, we were pleased to observe the fundamental role played by the solvent system upon the regioselective control in the presence of two different acidic amino groups (an aromatic and an aryl one): as depicted in Scheme 2, the use of 2-MeTHF dramatically improves the aromatic *N*-protection, leaving unaltered the alkyl amino group. However, this last example shows a remarkable effect of the temperature on the regioselectivity of the process: working at −50 °C in 2-MeTHF assures an excellent ratio between the monosilylated aniline **6** and the bis-silylated one **7** (90% *vs.* 4%), while it decreases at (78% *vs.* 14%) at 0 °C. On the other hand, the use of THF or diethyl ether affords uniquely a 1 : 1 mixture of both protected compounds, regardless the temperature (–78 °C, –50 °C). A possible explanation of this solvent-dependant regioselectivity is based on the different polarity of 2-MeTHF compared to diethyl ether and THF: in these latter solvents, the concomitant abstraction of the two different protons (the aryl-aminic one and the alkyl-aminic one) would afford a highly polar dianion that upon quenching with TBDMSCl would lead to the bis-silylated product **7**. On the other hand, in 2-MeTHF, the formation of this



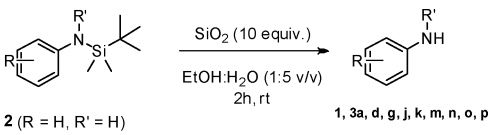
5 6 7

90% 4%

Scheme 2 *N*-TBS protection of an aniline bearing two distinct amino groups.

highly polar dianion is dramatically reduced as a consequence of the polarity of this solvent. It should be noted that in the case of 2-MeTHF, the time to reach completion noticeably increases from 0.5 to 3h, as a consequence of the low temperature maintained during all the course of the reaction.

In order to explore the compatibility of this protecting group with the 8th Principle of Green Chemistry, which states the need for protection-group free syntheses,[3] we developed a highly efficient removal of this same TBS group under very mild conditions: in fact, by simply stirring at room temperature the corresponding *N*-TBS-protected anilines in a suspension of silica gel in ethanol : water (1 : 5 v/v), starting anilines were recovered within 2 h in almost quantitative yields, without any need to purify them (Scheme 3). As can be seen, these deprotecting conditions are extremely useful for sensitive functionalities (ketones, esters, nitriles) that are not affected by this treatment, thus representing also a chemoselective procedure.



2 (R = H, R' = H)
4a (R = 2,3-$(CH_3)_2$, R' = H)
4d (R = 3,4-F_2, R' = H)
4g (R = 3-F-4-morpholino, R' = H)
4j (R = 4-Br, R' = H)
4k (R = 4-Ac, R' = H)
4m (R = 4-CN, R' = H)
4n (R = H, R' = CH_3)
4o (R = H, R' = Bn)
4p (R = H, R' = Ph)

1, 3a, d, g, j, k, m, n, o, p
quantitative

Scheme 3 Cleavage of the *N*-TBS group.

Conclusions

To conclude, we reported a highly efficient chemoselective preparation of highly stable *N*-TBS-arylamines under exceptionally milder reaction conditions (0 °C) than those previously described (–78 °C) by performing reactions in 2-MetHF, an eco-friendly and safer substitute of THF. This protocol presents a series of advantages, including uniformly excellent isolated yields in short reaction times and a remarkable effect of the solvent on the chemoselectivity and regioselectivity and of the process. The possibility to quantitatively remove the TBS group under mild and environmentally friendly conditions improves the usefulness of this protecting group in organic synthesis, thus overcoming the well-known drawback associated to the use of protecting-group, their low atom-economy. Thus, with this work we contribute not only to a progressive replacement of THF with its eco-friendly substitute MeTHF (which, as remarked in this work, presents a series of advantages over the former), but we also demonstrate that the use of the *N*-TBS protecting group allows to design a synthetic strategy in which the protection-deprotection steps do not influence negatively the process.

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