

# Unexpected formation of substituted anilides *via* reactions of trifluoroacetanilides with lithium reagents

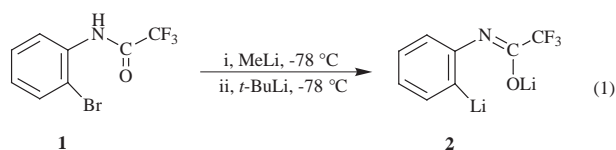
Keith Smith,\* Gamal A. El-Hiti† and Anna Hamilton

Department of Chemistry, University of Wales Swansea,‡ Swansea, UK SA2 8PP

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Reactions of trifluoroacetanilides with various organolithium reagents give the corresponding substituted anilides in good yields.

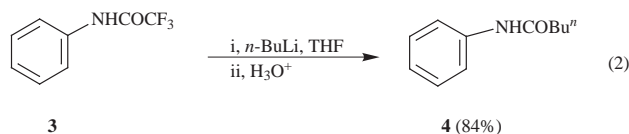
Dilithiotrifluoroacetanilide has recently been used as a synthetic intermediate in a variety of total syntheses of large natural products.<sup>1-4</sup> The dilithio reagent **2** was generated *via* deprotonation and bromine–lithium exchange from *N*-(2-bromophenyl)trifluoroacetamide (**1**) using a combination of methyl-lithium and *tert*-butyllithium [Eqn. (1)], according to a method originally developed by Wender and White.<sup>5</sup>



In one of the recent syntheses, an attempt was made to generate the dilithio reagent **2** directly from trifluoroacetanilide (**3**) using MeLi and *t*-BuLi.<sup>2</sup> However, reaction of the intermediate obtained with 2-bromoindan-1-one gave only 17% of the product and trifluoroacetanilide (80%) was recovered unreacted.

Because of our own interest in the use of doubly lithiated anilides and related compounds for organic synthesis<sup>6</sup> we also became interested in dilithio reagent **2** and wanted to obtain it directly from trifluoroacetanilide (**3**) so that the process could be more readily applied to other substituted trifluoroacetanilides. We therefore attempted the double lithiation of **3** with different lithiating reagents but could not achieve successful *ortho*-lithiation under any conditions we tried. With lithium diisopropylamide, no reaction occurred under the conditions tried. However, the reaction proceeded in an unexpected manner with alkylolithiums.

Thus, when **3** was reacted with *n*-BuLi (2 equiv.) in THF, valerianilide (**4**) was obtained in 84% yield after purification [Eqn. (2)]. *n*-BuLi had evidently acted overall as a nucleophile



rather than a lithiating agent, although it is likely that the mechanism involves initial deprotonation at nitrogen.

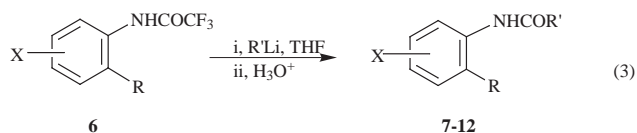
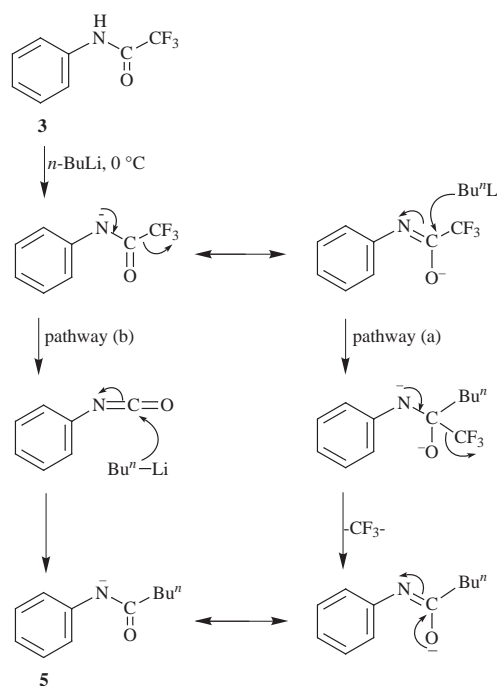
Following lithiation at nitrogen there are two alternative mechanisms to account for the product. One involves nucleophilic attack of the *n*-butyllithium at the carbonyl group, then elimination of trifluoromethyl anion to give monoanion **5** (pathway a, Scheme 1). The other involves elimination of trifluoromethyl anion to give phenyl isocyanate and then nucleophilic addition of *n*-butyllithium (pathway b, Scheme 1) to give the same anion, **5**. Protonation of anion **5** leads to the observed product, **4**.

The generality of the reaction was investigated by applying it to various substituted trifluoroacetanilides (**6**) and different lithium reagents; *n*-BuLi, PhLi and *t*-BuLi [Eqn. (3)]. The

**Table 1** Yields of substituted anilides from trifluoroacetanilides **6** according to Eqn. (3)

Product	R	R'	X	Yield (%) <sup>a</sup>	Mp (°C)
<b>4</b>	H	<i>n</i> -Bu	H	84	91–92 (lit., <sup>8</sup> 93)
<b>7</b>	Me	<i>n</i> -Bu	H	93	68–69 (lit., <sup>8</sup> 72–73)
<b>8</b>	Me	<i>n</i> -Bu	6-Me	60	Oil
<b>9</b>	H	Ph	H	77	131–132 (lit., <sup>8</sup> 131–132)
<b>10</b>	Me	Ph	H	71	158–160 (lit., <sup>8</sup> 145)
<b>11</b>	Me	Ph	6-Me	55	Oil
<b>12</b>	H	<i>t</i> -Bu	H	78	119 (lit., <sup>9</sup> 118–120)

<sup>a</sup> Yield of isolated, purified product.



yields of the isolated substituted anilides **7–12** are reported in Table 1.

As can be seen from Table 1, the reaction is reasonably general, accommodating substituents on the aniline ring and both alkyl and phenyl groups in the acyl moiety. This therefore represents another possible method for the synthesis of anilides.<sup>7</sup> Only reactions of *tert*-butyllithium proved to be not very general. As indicated, when unsubstituted trifluoroacetanilide **6** was reacted with *tert*-butyllithium, *N*-pivaloylaniline **12** was

obtained in 78% isolated yield. However, the reactions of *tert*-butyllithium with substituted trifluoroacetanilides **6** gave complicated mixtures of products under the general reaction conditions. We have not attempted to try to find conditions under which these reactions can give a single product.

## Conclusion

In many cases the reactions of trifluoroacetanilides with organolithium reagents lead to useful yields of anilides formally derived by replacement of the trifluoromethyl group by the organic group from the organolithium reagent.

## Experimental

### General procedure for the preparation of substituted anilides

To a cooled solution (0 °C) of substituted trifluoroacetanilide (1.0 mmol) in THF (10 ml) was added a solution of lithium reagent (2.0 mmol). The solution was stirred at 0 °C for 1 h and then left overnight at room temperature. The reaction mixture was diluted with ethyl acetate (10 ml) and quenched with saturated ammonium chloride solution (5 ml). The organic layer was separated, dried (MgSO<sub>4</sub>) and the solvent was removed under reduced pressure. The crude material was purified by column chromatography using dichloroethane–ethyl acetate (1:1) to give the substituted anilide.

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## Notes and references

† Permanent address; Department of Chemistry, Faculty of Science, Tanta University, Tanta, Egypt.

‡ Formerly known as the University College of Swansea.

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