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Three-Component Coupling Reactions of Thioformamides with Organolithium and Grignard Reagents Leading to Formation of Tertiary Amines and a Thiolating Agent

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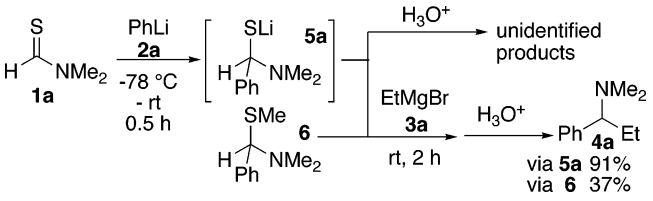
The development of new, multiple-component carbon−carbon bond-forming reactions is an important goal in synthetic organic chemistry. Recently, great interest has focused on three-component reactions that lead to formation of propargyl amines.[1] In earlier studies,[2] we found that thioiminium salts, derived from thioamides and methyl triflate, undergo sequential addition reactions with lithium acetylides and Grignard reagents. In the initial step of this process, thioamides are activated for nucleophilic addition of the organometallic reagents by complexation with the Lewis acid methyl triflate. Additional investigations revealed that methyl triflate activation is not required in reactions of thioformamides with a variety of organolithium compounds. Below, we describe the results of a recent effort that has led to the development of a new three-component coupling reaction of thioformamides. Sequential addition of organolithium and Grignard reagents to these substrates leads to the efficient production of tertiary amines. In addition, we have discovered that the byproduct of this process can be used as a novel thiolating agent.

On the basis of the well-known use of *N*,*N*-dimethylformamide (DMF) as a formylating agent in reactions with organolithium and Grignard reagents,[3] we have explored the use of *N*,*N*-dimethylthioformamide (**1a**) in similar reactions (Scheme 1).

By using NMR spectroscopy inspection of the mixture formed by reaction of this substance with phenyllithium (**2a**), followed by typical workup, showed that an unusual product containing phenyl and *N*,*N*-dimethylamino groups had formed.[4] Also, addition of ethylmagnesium bromide (**3a**) to the mixture, formed in the above process, led to the production of *N*,*N*-dimethyl *N*-1-phenylpropylamine (**4a**) in 91% yield. We reasoned that this transformation is initiated by formation of the lithium thiolate **5a**,[5] which then undergoes nucleophilic substitution by **3a** at the carbon atom bearing *N*,*N*-dimethylamino and LiS groups. The latter process is accompanied by elimination of the LiS group. In this reaction, the thioformamide thiocarbonyl carbon acts as dual electrophiles and the LiS group plays the formal role of a leaving group.[6] To evaluate the potentially unique leaving-group ability of LiS in this process, the *S*,*N*-acetal **6**[7] was reacted with **3a**. In this case, where SMe serves as the leaving group, the corresponding amine **4a** is obtained in only a low 37% yield. This result suggests that in substitution reactions with Grignard reagents, LiS is a better leaving group in **5a** than is MeS in **6**.

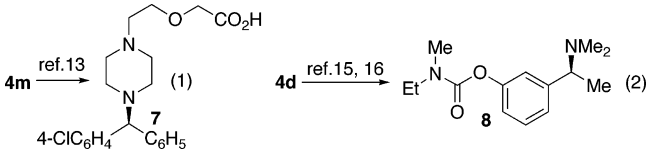
The wide applicability of this three-component reaction is demonstrated by the examples given in Table 1. Thioformamides, possessing morphoryl, *N*-Boc piperazyl, and *N*-Bn piperazyl groups (**1b**−**1d**), participate in this process. Notable observations are that the *N*-Boc group in **1c** is inert toward reaction with Grignard reagents even under reflux conditions in THF. In addition, selective introduction of organolithium reagents takes place at the carbon atom of the thioformyl group in **1c** (entries 11−15). In addition to phenyllithium (**2a**) (entries 1, 2, 8, 9, 11−13, 16, and 17), 2-furyl,

Scheme 1. Reaction of *N*,*N*-Dimethylthioformamide (**1a**) with Phenyllithium (**2a**) and Ethylmagnesium Bromide (**3a**)



2-pyridyl, ferrocenyl,[8] and 2-thienyl lithiums (entries 4−7, 14, 15, 18, and 19) can be used as reagents for this process. Reactions in which alkyllithiums participate are also highly efficient (entries 3 and 10). Likewise, a wide variety of alkyl, allyl, vinyl, and aryl magnesium reagents can be used. Halogen, dimethylamino, and methoxy substituents on the aromatic ring of arylmagnesium halides[9] do not influence the efficiency of this three-component reaction (entries 1−6, 8, 10−14). In all cases, products resulting from addition of two molecules of the organolithium reagent to the thioformamide are not observed even when an excess of the organolithium reagent is employed. The order of the addition of organolithium and Grignard reagent is very important. When the Grignard reagent is added to thioformamide first, followed by addition of the organolithium, the corresponding amine is not formed.

The three-component coupling reaction described above can be used to prepare several important tertiary amines, including diarylmethylpiperazines[10] (entries 11−14) which are among the most biologically important members of this family.[11] The synthesis of optically active cetilidine, **7**,[12] which is a H1-receptor antagonist, involves optical resolution of **4m** (eq 1).[13] Also, amine **4d**[14] is the key starting material in a sequence leading to racemic rivastigmine **8**, the optical resolution of which yields *S*-**8**[15] a drug used for the treatment of Alzheimer disease[17] (eq 2).



An interesting observation was made by careful inspection of the product mixture generated in these three-component reactions. Specifically, a light-yellow solid is formed when the reaction mixture is concentrated. To evaluate its characteristics, this solid was treated with acid chlorides (Scheme 2).

Reaction with benzoyl chloride leads to formation of thiobenzoic acid (**9**) in 92% yield, whereas reaction with phthaloyl dichloride gives phthalic thioanhydride (**10**) in 65% yield. On the basis of these observations, we propose that the solid is [LiSMgBr] and that this substance serves as a new thiolating agent.

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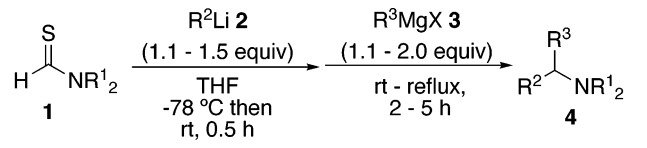
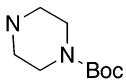
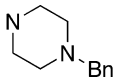
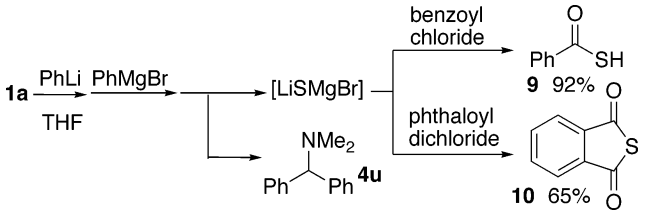
Table 1. Three-Component Coupling Reactions of **1**, **2**, and **3**[a]



entry	**1** NR^1_2	**2** R^2	**3** [b] R^3	product	yield(%)
1	NMe_2	Ph	4-$MeOC_6H_4$	**4b**	95[c]
2	**1a**	Ph	4-$Me_2NC_6H_4$	**4c**	91[d]
3		Me	3-$MeOC_6H_4$	**4d**	85[c]
4		2-Furyl	Ph	**4e**	86[c]
5		2-Pyridyl	Ph	**4f**	64[d]
6		Fc	Ph	**4g**	49[d]
7		Fc	Et	**4h**	66[d]
8	 **1b**	Ph	4-$MeOC_6H_4$	**4i**	94[c]
9		Ph	Allyl	**4j**	95[c]
10		*n*-Bu	4-$MeOC_6H_4$	**4k**	94[c]
11	 **1c**	Ph	4-FC_6H_4	**4l**	90[d]
12		Ph	4-ClC_6H_4 [e]	**4m**	85[d]
13		Ph	4-$MeOC_6H_4$	**4n**	85[d]
14		2-Thienyl	Ph	**4o**	83[d]
15		2-Thienyl	Et	**4p**	84[d]
16	 **1d**	Ph	Et	**4q**	77[d]
17		Ph	Allyl	**4r**	86[d]
18		2-Furyl	Vinyl	**4s**	69[d]
19		2-Furyl	*c*-Hex	**4t**	69[d]

[a] A THF solution of thioformamides **1** (1 mmol) was treated with organolithium **2** (1.1−1.5 equiv) and Grignard reagents **3** (1.1−2.0 equiv). [b] The X in **3** is Br unless otherwise noted. [c] The product was purified by acid−base workup. [d] The product was purified by column chromatography. [e] The X in **3** is Cl·LiCl.

Scheme 2. Reaction of in Situ Generated [LiSMgBr] with Acid Chlorides



In summary, the results of the investigation described above demonstrate that the three-component coupling reaction of thioformamides with organolithium and Grignard reagents serves as a novel and general method for the synthesis of tertiary amines. Since the organolithium and Grignard reagents used in this procedure are readily available,[18] this process stands as a highly versatile synthetic methodology. Moreover, the byproduct [LiSMgBr] formed in these reactions serves as a new thiolating agent. Further studies are underway probing the scope and applications of this methodology.

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Supporting Information Available: Experimental procedures and characterization of new compounds including spectral data. This material is available free of charge via the Internet at http://pubs/acs/org.

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