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Direct *N*-Acetyl Enamine Formation: Lithium Bromide Mediated Addition of Methyllithium to Nitriles

Cécile G. Savarin,* Geneviève N. Boice, Jerry A. Murry, Edward Corley, Lisa DiMichele, and Dave Hughes

Department of Process Research, Merck Research Laboratories, Merck & Company, P.O. Box 2000, Rahway, New Jersey 07065

cecile_savarin@merck.com

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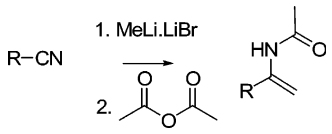
ABSTRACT



An improved protocol for *N*-acetyl enamine formation is disclosed which involves LiBr-mediated addition of MeLi to substituted nitriles. The resulting enamides are isolated in high yields and excellent purity which permits subsequent hydrogenation at very low catalyst loading.

Functionalized aryl enamides are important intermediates in synthetic organic chemistry. They are pivotal precursors for asymmetric hydrogenation to provide the corresponding chiral phenethylamines, which are widespread in natural products and medicinal agents.[1] Although a great deal of attention has been devoted to the development of new metal−ligand complexes for asymmetric hydrogenation, methods to access the required enamide precursors are limited. As a result, utilizing current literature methodology, practical enamide synthesis remains a challenge.

There are four common approaches to enamide preparations: (1) addition of an organometallic to an aryl nitrile (usually Grignard reagents) followed by a quench of the imine with the appropriate electrophiles,[2,1d] (2) reaction of an oxime with iron in the presence of Ac_2O,[3] (3) transition-metal-catalyzed coupling of vinyl derivatives with amide, and (4) the coupling of *N*-vinylacetamide with aryl halide (Scheme 1).[4] The first method, although the most direct, can provide complex reaction mixtures with low yields. In 1998,

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(4) (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (b) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1441. (c) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (d) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650. (e) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (f) Wallace, D.; Klauber, D. J.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749. (g) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845. (h) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (i) Klapars, A.; Campos, K. R.; Chen, C.-Y.; Volante, R. *Org. Lett.* **2005**, *7*, 1185. (j) Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277. (k) Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997. (l) Hansen, A. L.; Skrydstrup, T. *Org. Lett.* **2005**, *7*, 5585. (m) Qian, H.; Widenhoefer, R. A. *Org. Lett.* **2005**, *7*, 2635.

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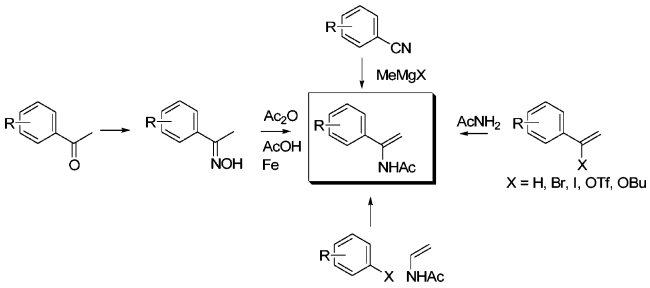
Scheme 1



Burk and Zhang reported an alternative protocol from ketones via the formation of an oxime followed by reaction with Fe/Ac_2O/AcOH. Yields with this protocol however remained low for a variety of substrates (25−56% yield from the ketone), and an additional oxime formation step is required. An alternative approach recently reported by several groups involves palladium- or copper-catalyzed coupling of vinyl halides/triflates with amides. Although these protocols appear to be high yielding and stereoselective, they require additional steps to form the necessary vinyl substrates or access to the properly functionalized coupling partners.

Despite the fact that the addition of an organometallic to a nitrile is the most direct approach, this method is usually not preferred due to complex reaction mixtures, irreproducible results, and low yields.[1d−e,5] We recently required an efficient synthesis of an aryl enamide (e.g., compound **1a**) and decided to further investigate the details associated with this method. In this communication, we report preliminary mechanistic studies of this complex transformation which laid the groundwork for the development of a robust, selective, and high-yielding methodology. We also describe a solution to the described problem with a methodology that affords enamides in high yield and purity from the corresponding nitriles.

We initiated our investigations by examining the addition of MeMgX to benzonitrile **2a** followed by a quench with an acetyl source. Following protocols disclosed in the literature, different sources of MeMgX (X = Br, Cl, I) were screened with and without various additives (CuX, MgX_2, $BF_3{-}OEt_2$) in different solvents (diethyl ether, THF, MTBE, toluene). Using MeMgBr, heat (50−60 °C) was required for the addition to take place and the enamide was obtained in 20−53% yield (Table 1, entry 1). MeMgI did not react at <0 °C, and at room temperature, only deprotection was observed. The use of a copper promoter improved the reaction yield slightly; however, the best yields were obtained with added LiBr and CuI and were about 60% (Table 1, entries 2−5). BOC deprotection was observed under all the conditions using the Grignard reagents, in addition to a small amount of dechlorination. In addition, careful analysis of the reaction profile by NMR and isolation of major side products revealed a complex reaction manifold, which is outlined in Scheme 2. Indeed, once the Grignard is added to the nitrile, metallo-

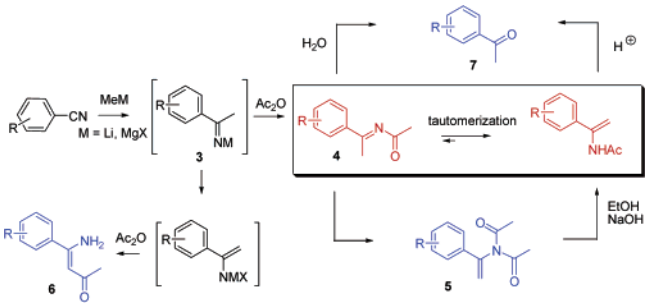
(5) Samuel, O.; Couffignal, R.; Lauer, M.; Zhang, S. Y.; Kagan, H. B. *Nouv. J. Chim.* **1981**, *5*, 15.

Table 1. Optimization with Various MeM

entry	conditions	yield (%)[a]
1	MeMgBr	20−53
2	MeMgBr, CuI	40−59
3	MeMgBr with added LiBr	55−58
4	MeMgBr, CuI with added LiBr	58−62
5	MeMgI	0[b]
6	MeLi	58−60
7	MeLi with added LiBr	82
8	MeLi−LiBr	86, 80[c]

[a] Assay yield. [b] No reaction was observed below 0 °C, and only deprotected product was observed at room temperature. [c] Isolated yield.

Scheme 2



imine **3** is first obtained and quenched with an acetyl group to generate acyl imine **4**. Under the standard enamide reaction protocols, the acyl imine **4** tautomerizes to the corresponding enamide upon warming to room temperature. Upon aqueous workup, the acyl imine is hydrolyzed to the corresponding ketone **7** so it is crucial to observe complete tautomerization to the enamide. In addition, significant amounts of C-acylated byproduct **6** and the bis-acylated enamide **5** were formed in the reaction.

With a better understanding of the reaction pathway and major side reactions that were occurring, we surveyed other reagents with the aim of modifying the course of the reaction. We turned our attention to MeLi (Table 1, entry 6), which gave a more reproducible and cleaner reaction profile than the corresponding Grignard reagent MeMgX, although the assay yields were still modest (58−60% yield).[6] With MeLi, at low temperatures, complete consumption of nitrile was observed in the absence of dechlorination or BOC removal but C-acylated byproduct **6** was still an important component in the mixture. Different sources of MeLi (MeLi in Et_2O, in cumene/THF, or in diethoxymethane) were investigated in

(6) Unlike with RMgX, Boc deprotection and dechlorination were not observed at low temperatures with MeLi. Screening conditions: (a) 0.8−1.5 equiv of MeLi at temperatures from −50 to +10 °C. (b) Ac_2O (1−2 equiv) in MTBE or toluene solution at temperatures from −50 to +10 °C.

several solvents, but none of these conditions provided significant yield improvement.[7] However, a screen of several inorganic additives revealed that the MeLi−LiBr complex afforded a much cleaner reaction profile, with 86% yield of the desired enamide obtained using the complex in ether (Table 1, entry 8). MTBE, Et_2O, and toluene gave similar yields and impurity profiles. Similar yields were also obtained using MeLi, adding separately 1 equiv of LiBr (Table 1, entry 7). Lower yields and more byproducts were obtained with less than 1 equiv of LiBr, including the C-acylated byproduct **6**. Byproduct **6** was also observed when the reaction was run in THF or while undercharging the MeLi−LiBr complex (0.8 equiv). No C-acylated product was observed under the optimum protocol which consisted of adding the MeLi−LiBr reagent to the nitrile in MTBE and aging the resulting mixture at low temperature (−10 to −30 °C). Upon complete disappearance of the nitrile, the mixture was cooled (−40 to −50 °C) before slow addition of Ac_2O in MTBE or toluene, maintaining the temperature lower than −30 °C. Quenching with neat Ac_2O or acetyl chloride led to complex reaction mixtures and a lower assay yield of enamide. No product was observed using EtOAc or MeOAc for the quench.

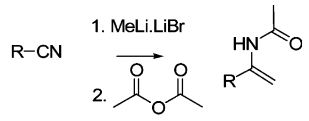
In some cases, the bis-acetylated enamide **5** was observed (even while using 1 equiv of Ac_2O). The bis-acetylated enamide could be easily converted to the desired enamide with an aqueous NaOH treatment in EtOH after the aqueous workup (Na_2CO_3 and NH_2OH worked equally well).[3c] Addition of acid (CH_3COOH, HCl) did not result in the desired transformation and in the case of HCl led mostly to hydrolysis to the ketone.

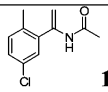
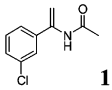
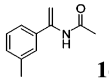
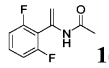
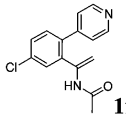
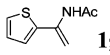
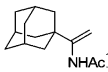
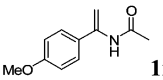
The role of LiBr in the reaction has not been fully established. We have been able to isolate a crystalline complex of nitrile **1a** with LiBr, which suggests lithium may be complexing the nitrile group to activate it toward nucleophilic addition. On the other hand, it is clear that LiBr plays a key role in the acetylation reaction, with greater amounts of C-acylation occurring in its absence. This suggests LiBr may be minimizing tautomerization of the metalloimine prior to the acetic anhydride quench. Further work on the role of LiBr is ongoing.

The reaction mixture was worked up using mild aqueous base ($NaHCO_3$ or K_2HPO_4).[8] Ketone **7** was a major byproduct when employing strong acidic quenches. Direct crystallization of the enamide from the resulting organic layer was accomplished from an EtOAc/MTBE/heptane mixture. Alternatively, the enamides could be crystallized from EtOH−H_2O to afford highly pure substrates for subsequent hydrogenation. It is important to note that the inorganic impurities from the enamide formation can often act as poisons in the subsequent catalytic hydrogenation reaction. As a result, an aqueous crystallization is usually preferred and advantageous.

With an optimized protocol established, we probed the scope and limitations of the improved enamide formation using the MeLi−LiBr complex.[9] The MeLi−LiBr procedure has been used to prepare various enamides in 60−85% yields (Table 2). The procedure worked with both electron-rich and -poor aryl nitriles with the corresponding enamides prepared in good yield. No dechlorination was observed with aryl chloride enamides (Table 2, entries 1, 2, and 5). Enamide **1f**, which could not be made with the oxime protocol, was obtained in good yield. In the case of enamide derived from

Table 2. Scope and Limitations



entry	product	yield (%)
1	 **1b**	90
2	 **1c**	70
3	 **1d**	73
4	 **1e**	85
5	 **1f**	76
6	 **1g**	60
7	 **1h**	79
8	 **1i**	62

(7) When the MeLi reaction is carried out at low temperature (−10 to −30 °C) and quenched cold (below −30 °C), the acyl imine **4** is observed as the major product. By working rapidly, we were able to isolate the acyl imine **4** prior to tautomerization by solvent evaporation at the end of the reaction and column chromatography purification. Of interest, these acyl imines, unlike the corresponding enamide, could also be reduced in situ by $NaBH_4$ affording the corresponding acetamide. An asymmetric reduction could be envisioned and will be the subject of future work.

(8) EtOAc was added during the workup to increase the solubility of the enamide.

(9) A typical experiment is as follows. Using a MeLi−LiBr complex: MeLi−LiBr is added to a cold solution (−10 to −30 °C) of the nitrile in MTBE (12 volumes). After aging the cold solution for 30−60 min, the solution is cooled to −40 to −50 °C and 5 M Ac_2O in MTBE is added slowly such that the temperature remains <30 °C. The reaction is warmed to room temperature, and after complete tautomerization of the acyl imine, the mixture is treated with EtOAc and aqueous K_2HPO_4. The solution is dried (Na_2SO_4), filtered, and evaporated to dryness. If diacetylated enamide is present, the solution is diluted with EtOH and treated with aqueous NaOH. Upon slow addition of H_2O, the enamide crystallizes out. Using MeLi: MeLi is added to a solution of the nitrile, LiBr, in MTBE (12 volumes) at cold temperatures (from −10 to −30 °C). The rest of the reaction proceeds as described above.

thiophene **1g**, this protocol represents a significant improvement over the low 15% yield isolated from reaction with methyl Grignard. Of interest, the adamantane substrate also converted efficiently to the corresponding enamide in 79% yield as compared to 43% yield using the oxime protocol.[3]

In summary, the formation of enamides via the addition of an organometallic species to a nitrile remains one of the most direct approaches. The low yields and complex reaction mixtures can be explained by studying the details of this complex reaction manifold. We have disclosed an improved protocol to aryl enamides in high yields (60−90%) which is applicable to ortho-substituted benzonitriles. The protocol has been extended to other enamides and is compatible with various functional groups including aryl chlorides and amine protecting groups. The enamides could be used in subsequent hydrogenation with low catalyst loading without requiring purification by column chromatography.

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Supporting Information Available: Experimental details, characterization, and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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