

Addition of Grignard Reagents to Aryl Acid Chlorides: An Efficient Synthesis of Aryl Ketones

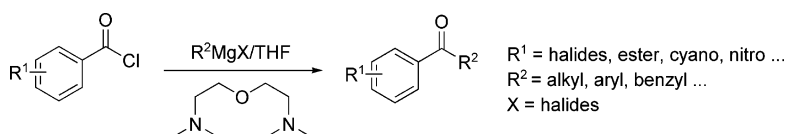
Xiao-jun Wang,* Li Zhang, Xiufeng Sun, Yibo Xu,
Dhileepkumar Krishnamurthy, and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc.,
Ridgefield, Connecticut 06877

xwang@rdg.boehringer-ingelheim.com

Received September 6, 2005

ABSTRACT



Direct addition of Grignard reagents to acid chlorides in the presence of bis[2-(*N,N*-dimethylamino)ethyl] ether proceeds selectively to provide aryl ketones in high yields. A possible tridentate interaction between Grignard reagents and bis[2-(*N,N*-dimethylamino)ethyl] ether moderates the reactivity of Grignard reagents, preventing the newly formed ketones from nucleophilic addition by Grignard reagents.

The acylation of organometallic reagents provides one of the most important synthetic routes to ketones¹ and is a central functionality in a variety of organic transformations, including regio- and stereospecific C–C bond formation. Generally, this is accomplished by reaction of an organometallic species with a functional carboxylic acid derivative, sometimes in the presence of a catalyst. One of the most attractive classes of organometallic compounds is represented by Grignard reagents, which have enjoyed an incredibly wide range of applications during their century-old history.² These reagents are typically reacted with a range of active amides, esters, thioesters, and anhydrides.³ Acid chlorides are by far the cheapest and industrially most attractive acylating agents, and ketone syntheses involving these substrates include the palladium-catalyzed coupling with organostannanes⁴ and borates,⁵ the acylation of organocoppers and zincs reagents,⁶

as well as derivatives of silicon,⁷ manganese,⁸ indium,⁹ mercury,¹⁰ zirconium,¹¹ rhodium,¹² and many others.¹³ Although Ni(II)- and Fe(III)-catalyzed additions of Grignard reagents to acid chlorides have also been reported,¹⁴ to date, there is no general approach to ketones by the direct, non-

(4) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417.

(5) (a) Negishi, E.; Idacavage, M. *J. Org. React.* **1985**, *33*, 1. (b) Cho, C. S.; Itotani, K.; Uemura, S. *J. Organomet. Chem.* **1993**, *433*, 253.

(6) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1983**, *24*, 5081. (c) Wehmeyer, R. M.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 4513. (d) Takai, K.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1281. (e) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (f) Tamaru, Y.; Ochiai, H.; Sanda, F.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5529. (g) Sato, F.; Kodama, H.; Tomura, Y.; Sato, M. *Chem. Lett.* **1979**, 623. (h) Fujisawa, T.; Mori, T.; Higuchi, K.; Sato, T. *Chem. Lett.* **1983**, 1791. (i) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (j) Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106. (k) Rozen, S.; Shahak, I.; Bergmann, E. D. *Synthesis* **1972**, 701.

(7) (a) Olah, G. A.; Ho, T. I.; Prakash, G. K. S.; Gupta, B. G. B. *Synthesis* **1977**, 677. (b) Karpov, A. S.; Muller, T. *J. Org. Lett.* **2003**, *5*, 3451.

(8) (a) Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 7369. (b) Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1992**, *33*, 4439. (c) Kim, S.-H.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 2322.

(9) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963.

(10) Larock, R. C.; Lu, Y. *J. Org. Chem.* **1993**, *58*, 2846.

(11) (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115. (b) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 638. (c) Wipf, P.; Xu, W. *Synlett.* **1992**, 718.

(12) Hegedus, L. S.; Kendall, R. M.; Lo, S. M.; Sheats, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 5448.

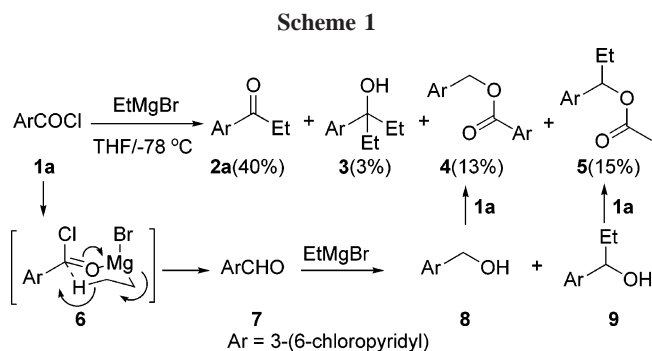
(1) (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989. (b) Groves, J. K. *Chem. Soc. Rev.* **1972**, *1*, 73. (c) Shirley, D. A. In *Organic Reactions*; Wiley: New York, 1954; Vol. 8, p 28.

(2) (a) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995. (b) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996.

(3) (a) Meyer, A. I.; Comins, D. L. *Tetrahedron Lett.* **1978**, *19*, 5179. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (c) Staab, H. A.; Jost, E. *Ann. Chem.* **1962**, 655, 90. (d) Sakan, T.; Mori, Y. *Chem. Lett.* **1972**, 793. (e) Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763. (f) Araki, M.; Mukaiyama, T. *Chem. Lett.* **1974**, 663.

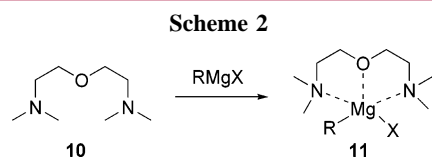
transition-metal-catalyzed or -promoted addition of Grignard reagents to acid chlorides.

Despite a report of addition of Grignard reagents to acid chlorides at low temperature,¹³ our experience matches that of others¹⁴ in obtaining unsatisfactory results with this direct procedure: as expected, we were faced with low yields of ketones and many side reactions. Such side reactions are summarized in Scheme 1: addition of ethylmagnesium



bromide to **1a** in THF at $-78\text{ }^{\circ}\text{C}$ produced the desired ketone **2a** in only 40% yield along with a small amount of **3** and two major side products **4** (13%) and **5** (15%), both from the reduction of **1a** by EtMgBr through β -elimination of complex **6**.¹⁷

Our approach to developing a general method for the *direct* (i.e., without transition-metal catalysts) synthesis of ketones from acid chlorides and Grignard reagents involved moderating the reactivity of the organomagnesium reagent by complexation with a simple organic ligand. We now report that a simple tridentate ligand such as **10** is capable of complexing Grignard reagent to provide a complex, proposed as **11** (Scheme 2),¹⁸ and addition of this complex to a wide



range of acid chlorides affords aryl ketones in good to excellent yields.

Our expectation that ligand **10** may be able to moderate the nucleophilicity of Grignard reagents was confirmed by

(13) (a) Burkhardt, E. R.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 416. (b) Marko, I. E.; Southern, J. M. *J. Org. Chem.* **1990**, *55*, 3368. (c) Hirao, T.; Misu, D.; Yao, K.; Agawa, T. *Tetrahedron Lett.* **1986**, *27*, 929. (d) Han, Y.; Fang, L.; Tao, W.-T.; Huang, Y.-Z. *Tetrahedron Lett.* **1995**, *36*, 1287. (e) Zhang, I.-J.; Huang, Y.-Z.; Jiang, H.-X.; Duan-Mu, J.; Liao, Y. *J. Org. Chem.* **1992**, *57*, 774. (f) Kasatkin, A. N.; Kulak, A. N.; Tolstikov, G. A. *J. Organomet. Chem.* **1988**, *346*, 23.

(14) (a) Cardellicchio, C.; Flandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053. (b) Inaba, S.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373. (c) Malanga, C.; Aronica, L. A.; Lardicci, L. *Tetrahedron Lett.* **1995**, *36*, 9185.

our preliminary observation that a 1:1 mixture of PhMgBr and **10** in THF did not react with benzophenone even at $0\text{ }^{\circ}\text{C}$. We were delighted to observe that our concept could be experimentally confirmed: addition of the 1:1 mixture of EtMgBr and **10** to acid chloride **1a** in THF at $-60\text{ }^{\circ}\text{C}$ gave ketone **2a** in 91% isolated yield (entry 1, Table 1). The side

Table 1. Addition of Alkylmagnesium Halides to Acid Chlorides in the Presence of **10**

entry	acid chloride	Grignard	product	isolated yield
1		EtMgBr		91%
2		EtMgBr		84%
3		EtMgBr		77%
4		PrMgCl		85%
5		iPrMgCl		76%
6		iPrMgCl		75%
7		MeMgBr		69%
8		PhCH ₂ MgCl		92%
9		PhCH ₂ MgCl		85%
10				80%

products **4** and **5**, as well as the tertiary alcohol **3** resulting from double addition, were not detected. We explored a wide

(15) Sato, F.; Inoue, M.; Oguro, K.; Sato, M. *Tetrahedron Lett.* **1979**, *20*, 4303.

(16) For examples, see: (a) Hoffmann, R. W.; Hölzer, B. *J. Am. Chem. Soc.* **2002**, *124*, 4204. (b) Cánepa, A. S.; Bravo, R. D. *Synth. Commun.* **2004**, *34*, 579.

(17) Maeda, H.; Okamoto, J.; Ohmori, H. *Tetrahedron Lett.* **1996**, *37*, 5381.

(18) Diamines and polyethers have been used to complex Grignard reagents, and the resulting complexes, where Mg coordination ranges from 4 to 6, have been characterized spectroscopically and by X-ray crystallography; see: Uhm, H. L. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; p 117.

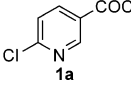
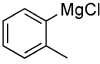
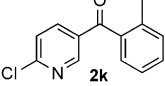
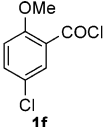
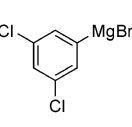
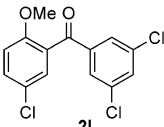
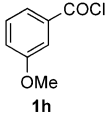
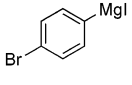
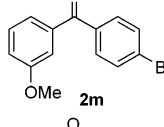
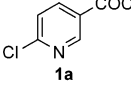
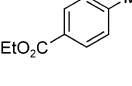
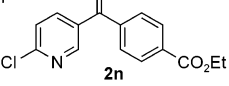
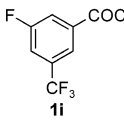
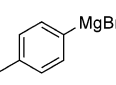
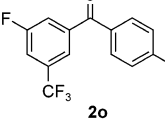
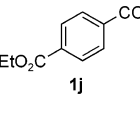
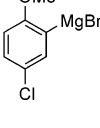
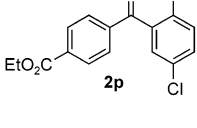
range of alkyl Grignard reagents and acid chlorides in the coupling reaction, as shown in Table 1. Whereas primary alkylmagnesium halides produced excellent yields of ketones, α -branched ones provided slightly lower yields. Benzyl Grignard reagents afforded results as good as those of primary counterparts. It is noteworthy that coupling of MeMgBr–**10** complex with acid chloride **1f** (entry 7) proceeded only at a higher temperature ($-35\text{ }^{\circ}\text{C}$),¹⁹ implying a less reactive MeMgBr–**10**, perhaps due to more effective chelation. This hypothesis is in agreement with the fact that α -branched, and therefore, more hindered, Grignard reagents exhibited a higher degree of side products (entries 5 and 6, Table 1). A number of functional groups, including the nitro group, are tolerated under the reaction conditions. Based on the fact that excellent yields of aryl ketones were obtained with the use of only a slight excess of the organomagnesium complexes (1.1–1.3 equiv), one can conclude that there was no competing enolization of the resulting ketones, even in the cases of benzylic ketones (entries 8 and 9, Table 1).²⁰

Greatly encouraged by our initial studies, we next examined a number of aromatic Grignard reagents in this new coupling reaction, with the aim of developing a general synthesis of benzophenone analogues. We were again rewarded by the observation that addition of the 1:1 mixture of arylmagnesium halides and **10** in THF to a number of acid chlorides proceeded smoothly at $-5\text{--}0\text{ }^{\circ}\text{C}$ (1–5 h) to produce benzophenones in good to excellent yields (Table 2). The coupling reactions did not occur at low temperature ($<-20\text{ }^{\circ}\text{C}$).

As a test for the importance of the proposed tridentate complexation between Grignard reagents and **10**, we used *N*-methylmorpholine, bidentate TMEDA, and tridentate *N,N,N',N',N''*-pentamethyldiethylenetriamine (**12**) as alternative ligands in the coupling. As we expected, while **12** showed effectiveness similar to that of **10**, TMEDA produced a higher degree of side reactions, and NMM has no effect at all.

In conclusion, we have described a new protocol for the general synthesis of aryl ketones by acylation of Grignard reagents with aromatic acid chlorides in the presence of bis[2-(*N,N*-dimethylamino)ethyl] ether.²¹ Although a definitive

Table 2. Addition of Arylmagnesium Halides to Acid Chlorides in the Presence of **10**

entry	acid chloride	Grignard	product	isolated yield
1				88%
2				85%
3				80%
4				87%
5				71%
6				84%

evidence for the interaction between Grignard reagents and **10** or **12** reported here is not yet at hand, the existence of a complex can be inferred by the modified reactivity observed. Further studies may shed some light on the nature of the reactive species. Furthermore, the concept of altering the reactivity of Grignard reagent can be utilized in number of other transformations, and these are currently under active investigation.

Supporting Information Available: A typical experimental procedure and spectroscopic data for all new compounds **2a–c,h–p**, **4**, and **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL052150Q

(19) Double addition product was detected.

(20) Hatano, M.; Matsumura, T.; Ishihara, K. *Org. Lett.* **2005**, *7*, 573.

(21) Addition of Grignard reagent–**10** complexes to α -branched aliphatic acid chlorides leads to ketones in moderate to good yields, which is still under investigation.