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# Iron-Catalyzed Cross-Coupling of Imidoyl Chlorides with Grignard Reagents

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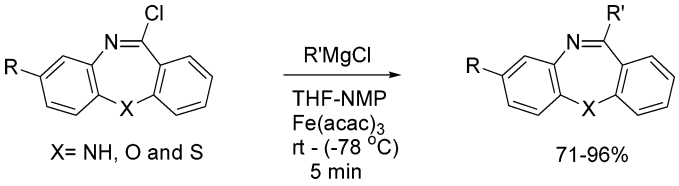
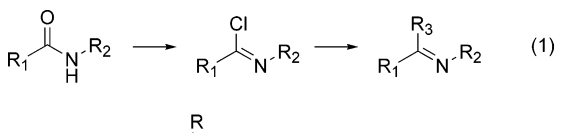
## ABSTRACT

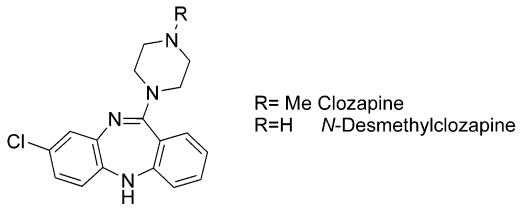



**A general, high yielding rapid iron-catalyzed cross-coupling reaction between Grignard reagents and imidoyl chlorides is described. These reactions are typically completed within 5 min, resulting in high yields of 71–96% using 5% iron catalyst in a THF–NMP solvent mixture. Functionalized imidoyl chlorides (e.g., R = $CO_2Me$) gave excellent yields (89%).**

Herein, we report a study of the first iron-catalyzed cross-coupling reactions between imidoyl chlorides and Grignard reagents. These reactions, which mainly lead to the formation of an $sp^2-sp^3$ carbon−carbon bond are fast, mild, and frequently high yielding. Surprisingly, few metal-catalyzed cross-coupling reactions of imidoyl chlorides have been studied and those reported so far have used expensive Pd[1] or toxic Ni[2] catalysts. In contrast, the iron catalysts used herein are inexpensive, toxicologically benign, and easy to handle.[3] The iron-catalyzed cross-couplings provide an attractive means of using an amide bond as a synthon for carbon−carbon bond formation, via an intermediate imidoyl chloride (eq 1). Recently, Nadin et al. reported one example of a metal-catalyzed imidoyl chloride cross-coupling generating an $sp^2-sp^3$ bond, a Pd-catalyzed Negishi reaction.[1a]




(1)




In this report, we use the iron-catalyzed cross-coupling reaction to synthesize analogues of clozapine, an approved antipsychotic drug, and its metabolite *N*-desmethylclozapine.[4] In the initial studies, *n*-BuMgCl was added to imidoyl chloride **1** generated from the corresponding lactam[5] (Table 1). Both TLC and GC/MS analyses showed a completed reaction after 30 min at ambient temperature in THF, and the butyl derivative **2** was obtained in 42% yield (entry 1). Decreasing the reaction temperatures gave extended reaction

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(3) (a) Blom, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217−6254. (b) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624−629. For iron-catalyzed cross-coupling of 2-(hetero)aryl chlorides: Fürstner, A.; Leitner A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863.

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(5) For synthesis, see Supporting Information.

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**Table 1.** Iron-Catalyzed Cross-Coupling of Imidoyl Chloride **1**


**1** **2-7**

| entry | R | solvent/catalyst | temp/time (min) | yield (%)[a] |
|---|---|---|---|---|
| 1 | *n*-Bu (**2**) | THF/ - | rt/30 | 42 |
| 2 | *n*-Bu (**2**) | THF/$Fe(acac)_3$ | rt/5 | 22 |
| 3 | *n*-Bu (**2**) | THF−NMP/$Fe(acac)_3$ | rt/5 | 96 |
| 4 | *n*-Bu (**2**) | THF−NMP | rt/30 | 20 |
| 5 | *n*-Bu (**2**) | THF−NMP/$Fe(acac)_3$ | −78 °C/5 | 94 |
| 6 | *n*-Bu (**2**) | THF−NMP/$FeCl_3$ | rt/5 | 96 |
| 7 | cyclohexyl (**3**) | THF−NMP/$Fe(acac)_3$ | rt/5 | 93 |
| 8 | *t*-Bu (**4**) | THF−NMP/$Fe(acac)_3$ | rt/5 | 27 |
| 9 | 1,3-dioxan-2-ylethyl (**5**) | THF−NMP/$Fe(acac)_3$ | rt/5 | 95 |
| 10 | Me (**6**) | THF−NMP/$Fe(acac)_3$ | rt/5 | 17 |
| 11 | $Me_3SiCH_2$ | THF−NMP/$Fe(acac)_3$ | rt/5 | 0 (72)[b] |
| 12 | Ph (**7**) | THF−NMP/$Fe(acac)_3$ | rt/30 | 55[c] |

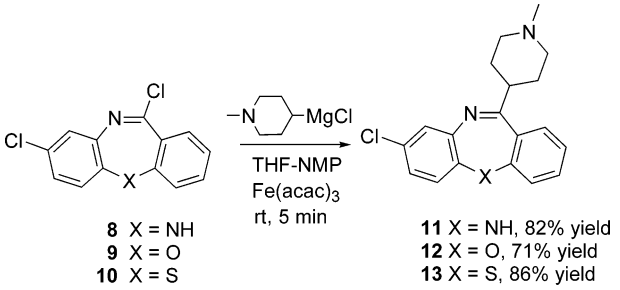
[a] Isolated yields. [b] The yield in the parentheses refers to R = Me, the desilylated product **6**. [c] With 6 equiv of the Grignard reagent.

times, and at −40 °C, no reaction was observed. Adding an iron catalyst ($Fe(acac)_3$, 5 mol %) to the reaction mixture increased the reaction rate; at room temperature, the imidoyl chloride **1** was consumed within 5 min. Disappointingly, the iron-catalyzed reaction gave a lower yield (22%) compared with the 42% yield obtained in the uncatalyzed reaction (entry 2 vs 1). However, using a THF-*N*-methyl-2-pyrrolidinone (NMP) solvent mixture reported by Cahiez et al.,[6] an excellent isolated 96% yield of compound **2** was achieved (entry 3). Using the THF−NMP solvent mixture, iron-free reaction conditions still generated a low yield (20%) of **2** (entry 4). This confirmed the significance of the iron catalyst in the high yielding, rapid reactions. Even at −78 °C, using the previously detailed iron-catalyzed conditions, the reaction was completed within 5 min, with a 94% isolated yield (entry 5). Furthermore, the iron catalysts $FeCl_3$ and $Fe(acac)_3$ were interchangeable, with no difference in the reaction outcome observed using either catalyst at room temperature (entries 3 and 6).

The reaction between the more sterically demanding cyclohexylmagnesium chloride and imidoyl chloride **1** afforded derivative **3** in an excellent, isolated 93% yield (entry 7). Encouragingly, under standard conditions, the sterically encumbered *t*-BuMgCl still gave product **4** (entry 8), although only in low yield (27%). The functionalized Grignard reagent, (1,3-dioxan-2-yl)ethylmagnesium chloride, gave **5** in 95% yield (entry 9). Methylmagnesium chloride failed to efficiently react, giving **6** in a low yield (17%) with major recovery of starting material.[7] Interestingly, the ((trimethylsilyl)methyl)magnesium chloride (entry 11) gave the desilylated methyl product **6** as the sole product in 72% yield. No silylated product was detected in the reaction mixture according to GC/MS analysis. $Me_3SiCH_2MgCl$ has successfully been used in iron-catalyzed cross-coupling with alkenyl triflate generating the corresponding silyl-functionalized compound.[7] Furthermore, adding PhMgCl to **1**, creating an $sp^2-sp^2$ carbon−carbon bond, gave ca. 55% yield of **7** with all the tested solvents, i.e., THF, THF−NMP, and $Et_2O$. The lower yield compared with aliphatic reagents is explained by a competing homocoupling of the aryl Grignard reagent producing biphenyl.[8] No reaction took place between ethynylmagnesium bromide and **1** using the iron-catalyzed conditions developed for alkyl Grignards.

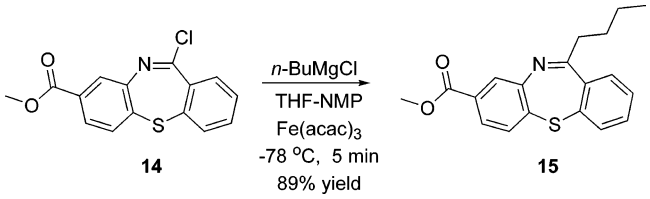
By focusing on clozapine analogues, imidoyl chlorides **8**−**10**[5] reacted with *N*-methyl-piperidinylmagnesium chloride[9] to give azepines **11**−**13** in good yields (71−86%, Scheme 1).[10] This also showed that basic amines were compatible with the reaction conditions.

**Scheme 1.** Synthesis of Clozapine Analogues




The mild reaction conditions (−78 °C and 5 min reaction time, entry 5) indicated the possibility of having additional functionalities present during the reaction.[11] The ester derivative **14** was reacted with *n*-BuMgCl at −40 °C for 5 min, which resulted in selective formation of **15** in an excellent 89% yield (Scheme 2). No products from the anticipated competing addition to the ester functionality were isolated. Running the reaction in the absence of $Fe(acac)_3$ at −10 °C gave a complex product mixture.

**Scheme 2.** Reaction between the Grignard Reagent and Ester-Functionalized Imidoyl Chloride




A Weinreb amide-functionalized imidoyl chloride **16** selectively reacted either at the imidoyl chloride or at the

(6) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.
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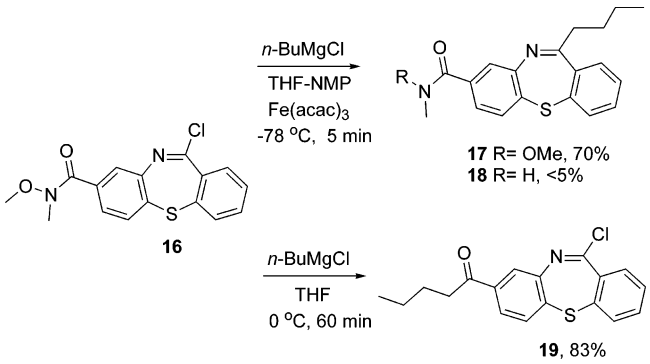
(8) (a) Cahiez, G.; Chaboche, C.; Mahutesu-Betzer, F.; Arh, M. *Org. Lett.* **2005**, *7*, 1943−1943. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491−493.
(9) Engelhardt, E. L.; Zell, H. C.; Saari, W. S.; Christy, M. E.; Dylion Colton, C. *J. Med. Chem.* **1965**, *8*, 829−835.

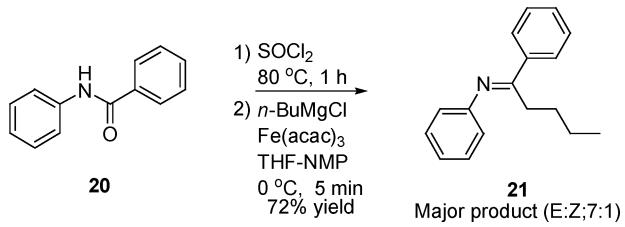
Weinreb amide depending on the reaction conditions used (Scheme 3). The $Fe(acac)_3$-catalyzed reaction gave **17** in 70% yield,[12] and the major byproduct (5%) was the demethoxylated amide **18**.[13] Selective addition to the Weinreb amide (**16**) was achieved in 83% yield, to afford **19**, by applying standard Grignard reaction conditions at 0 °C in THF, in the absence of the iron catalyst.

**Scheme 3.** Selective Addition of Grignard Reagents Discriminating between Weinreb Amide and Imidoyl Chloride Functionalities




As demonstrated in Scheme 4, the iron-catalyzed reaction is not limited to cyclic compounds. Imine **21**[14] was synthesized from amide **20** in 72% yield over two steps using standard conditions. The intermediate imidoyl chloride was concentrated at reduced pressure and used in the following cross-coupling without further purification.

**Scheme 4.** Synthesis of Imine **21**




In summary, we have developed a general, high yielding, rapid iron-catalyzed cross-coupling reaction between Grignard reagents and imidoyl chlorides. Under the mild reaction conditions, functionalities such as esters are unaffected. Selective additions of Grignard reagents at either the Weinreb amide or the imidoyl chloride functionality were achieved in a substrate incorporating both. Applying the herein developed conditions on a privileged core structure gave facile access to bioisosteric analogues of clozapine. In addition, the mild reaction conditions make this protocol an efficient alternative for the synthesis of imines compared to the forced conditions normally used in condensation reactions.

**Acknowledgment.** We thank Mrs. Sine Mandrup Bertozzi for expert analytical assistance.

**Supporting Information Available:** Synthetic procedures and the characterization of compounds **1**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The dibenzodiazepine clozapine analogue **11** has been specifically exemplified and claimed in the patent literature together with some other close piperidyl clozapine analogues. Although a generic synthetic methodology was described (the final step was a condensation reaction giving the imine functionality using phosphorus pentoxide in phosphorus oxychloride at reflux overnight), no physical data supporting the claimed structure **11** was presented. Hardy, R. A., Jr. 11-(4-Piperidyl)dibenzodiazepines. US4045445, 1977.

(11) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901−1904.

(12) Only 0.95 equiv of Grignard reagent was used because of the competing demethoxylation reaction. The use of 2 equiv of Grignard reagent gave **18** in 66% yield.

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