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Reactions between Weinreb Amides and 2-Magnesiated Oxazoles: A Simple and Efficient Preparation of 2-Acyl Oxazoles

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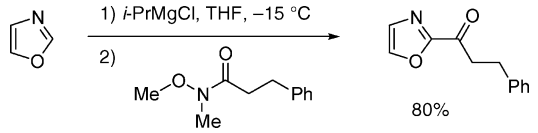
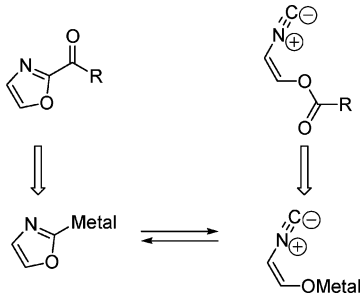


Treatment of oxazole or 5-aryl oxazoles with *i*-PrMgCl smoothly generates the corresponding 2-Grignard reagents, which react with Weinreb amides to provide exclusively 2-acyl oxazole products.

The oxazole motif occurs within the framework of numerous important pharmacophores, natural products, and synthetic intermediates.[1] In light of this significance, numerous syntheses of variously substituted oxazoles have been developed, with Robinson−Gabriel cyclodehydration methods gaining wide popularity.[2] A fascinating subfield of oxazole chemistry involves C2 functionalization of preformed oxazole cores.[3] In fact, for more than 30 years, chemists from various groups the world over have been motivated and intrigued by the peculiarities of 2-metalated oxazoles and their subsequent reactions.[4]

It has been conclusively established through both solution NMR spectroscopy and solid-state structural characterization that 2-lithio-oxazoles exist predominantly as ring-opened enolate isonitriles and not as the expected cyclic structures (Scheme 1).[5] The outcome of reactions between these metalated intermediates and electrophiles is highly dependent on the nature of the electrophile. The formation of the expected 2-substituted

SCHEME 1. The Isomeric Forms of Metalated Oxazole and Subsequent Reactions with Acylating Agents



oxazoles in some cases (e.g., deuterium oxide, trimethylsilyl triflate, benzaldehyde) demonstrates that the two forms are in equilibrium, despite the thermodynamic dominance of the ring-opened form.[6]

The 2-acyl oxazole product family represents a specialized challenge within this research area, and several attempts have been made to provide a general entry into this class of compounds. Direct reaction of the organolithium species with acyl chlorides results in the corresponding O-acylated ring-opened products.[7] Two-step approaches involving initial reaction with an aldehyde and subsequent oxidation have been more successful.[6b] A particularly clever iteration of this strategy involves precomplexation of the oxazole with borane to provide a species that reacts through its closed form.[8]

The most successful synthesis of 2-acyl oxazoles to date has been published by workers at Eli Lilly.[9] An initially formed lithiate is transmetalated to the zincate, and then permitted to react with an acyl chloride in the presence of stoichiometric copper iodide. The success of this approach stems from the fact that, unlike the corresponding lithiates, oxazole zincates exist in their closed form. Calculations suggest that the structural discrepancies result primarily from differences in the hybridization about carbon for the two types of organometallic reagents.[5c]

Despite the progress, the state-of-the-art for acyl oxazole synthesis remains less than ideal. Charged with providing multigram quantities of a potential new drug candidate bearing this structural motif, we became interested in developing a new approach to 2-acyl oxazoles. Because of the reported instability of 2-lithio oxazoles in THF at temperatures above −40 °C,[10] our first priority was to determine an alternative metal counterion. On the basis of recently reported successful applications of Grignard oxazole reagents in reactions with iminium or trimethylsilyl triflate reagents,[11] we undertook to characterize the solution structure of these species at 0 °C in THF. In the

(1) For leading references on oxazoles, see: (a) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389−437. (b) Boyd, G. V. *Science of Synthesis*; Schaumann, E., Ed.; Georg Thieme Verlag: New York, 2001; Vol. 11, Chapter 12, pp 383−479. (c) Iddon, B. *Heterocycles* **1994**, *37*, 1321−1346.

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(4) Schroder, R.; Schollkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533−546.

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(6) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1987**, *52*, 3413−3420. (b) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058−3063. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Mastellari, A.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1984**, *49*, 3478−3483. (d) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449−452.

(7) Dondoni, A.; Dall'Occo, T.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Chem. Soc., Chem. Commun.* **1984**, 258−260.

(8) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192−5198.

(9) (a) Harn, N. K.; Gramer, C. J.; Anderson, B. A. *Tetrahedron Lett.* **1995**, *36*, 9453−9456. (b) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583−585.

(10) Reeder, M. R.; Gleaves, H. E.; Hoover, S. A.; Imbordino, R. J.; Pangborn, J. *J. Org. Process Res. Dev.* **2003**, *7*, 696−699.

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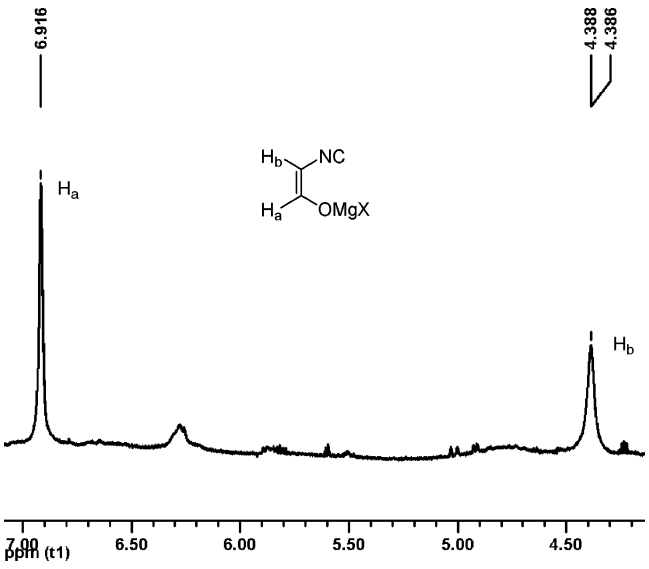


FIGURE 1. ^{1}H NMR spectrum of magnesiated oxazole in THF at 0 °C.

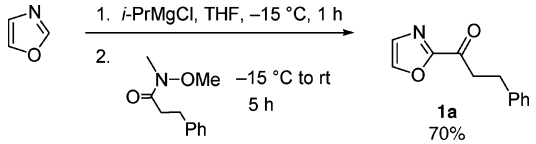
case of the ring-opened lithiate, ^{1}H NMR shifts of 6.95 and 4.42 ppm have been reported (THF, rt), while in the case of the ring-closed zincate, shifts of 8.1 and 7.4 ppm have been reported (THF, rt).[12] Our observation of 6.92 and 4.38 ppm strongly suggests that the magnesiate exists primarily in the open form, analogous to the lithiate.

Since these oxazole magnesiates exist predominantly as ring-opened enolates, any subsequent reaction to provide closed ring products would necessarily proceed through a dynamic kinetic resolution (Scheme 1). In other words, the rate of reaction with an electrophile would need to be slower than the rate of equilibration between the open and closed form of the intermediate magnesiate. Because we were interested specifically in reactions to form aliphatic acyl oxazoles, we were also concerned about the quenching of our organometallic species by α-deprotonation of the desired products. Weinreb amides possess an attenuated reactivity toward initial addition, and the resulting tetrahedral intermediates are often stable until subsequent workup.[13]

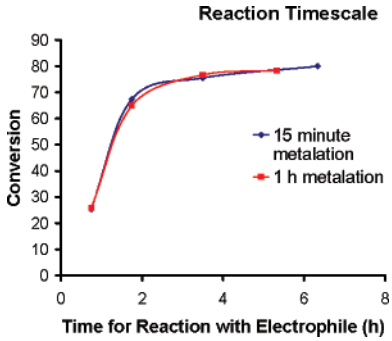
With this reasoning as a backdrop, we found that treatment of oxazole (1.25 equiv) with *i*-PrMgCl (1.25 equiv) at −15 °C in THF, followed by reaction with the Weinreb amide of hydrocinnamic acid at room temperature (1 equiv) provided the desired product **1a** in 70% yield (Scheme 2).

Encouraged by this initial success, we sought to further evaluate the reaction with respect to the time scale for metalation and the time scale for reaction with electrophile. Shown graphically in Scheme 3 are results obtained from reaction monitoring of the product-forming step in the synthesis of **1a**

SCHEME 2. Test Reaction for the Construction of 1a



SCHEME 3. Determination of Relevant Reaction Time Scales in the Formation of 1a (−15 °C metalation, warm to rt for reaction with Weinreb amide)[a]



[a] Both reactions were run as follows: 1.25 equiv of oxazole; 1.25 equiv of *i*-PrMgCl (2 M in THF), 1 equiv of Weinreb amide. Conversions were determined by quantitative HPLC analysis of reaction mixtures.

for two separate reactions. In one case, the reaction was aged for 15 min after addition of *i*-PrMgCl, while in the other case it was aged for 1 h. From the comparability of the two reactions, we deduced that the metalation was complete after a very short period of time (15 min or less), while the subsequent reaction with electrophile was determined to require greater than 6 h. HPLC analyses of these reactions revealed only product and starting materials.

We also determined a preferred concentration for the reaction with 0.14 M oxazole in THF providing **1a** in 82%. A reaction at higher concentration (0.28 M) resulted in a yield of 71%; reaction at a lower concentration (0.11 M) provided the product in just 62% yield. During our studies, we also found no deleterious effect when utilizing 2 M *i*-PrMgCl in diethyl ether relative to reactions executed with 2 M *i*-PrMgCl in THF (87% and 82% yield, respectively). Finally, we found that due to solubility problems, THF was a vastly superior solvent to MTBE or toluene. Employment of the latter two solvents resulted in no product formation.

With optimized conditions in hand, we next turned to evaluating the scope of the reaction with respect to electrophilic partners (Table 1). Simple unbranched alkyl Weinreb amides (entries 1 and 2), including an example with a terminal *N*-Boc-piperidine (entry 3), were all successful electrophiles in this reaction. Increased steric hindrance in the form of α-branching did not shut down the reaction (entry 4); even an α-oxygenated Weinreb amide was successful in this reaction, albeit in attenuated yield (entry 5). Both vinyl and aryl Weinreb amides were employed with excellent results, as well (entries 6 and 7).[14] Less successful was a reaction between oxazole Grignard and a pre-deprotonated α-Boc-amino-Weinreb amide (entry 8).[15]

(11) (a) Ikemoto, N.; Miller, R. A.; Fleitz, F. J.; Liu, J.; Petrillo, D. E; Leone, J. F.; Laquidara, J.; Marcune, B.; Karady, S.; Armstrong, J. D., III; Volante, R. P. *Tetrahedron Lett.* **2005**, *46*, 1867−1871. (b) Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A. *Tetrahedron Lett.* **2002**, *43*, 935−938.

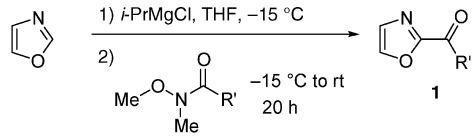
(12) Proton NMR data for the oxazole lithiate and zincate may be found in refs 5a (lithiate and zincate) and 5d (lithiate). Carbon NMR data for the oxazole lithiate and the benzoxazole zincate may be found in ref 5b.

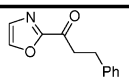
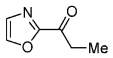
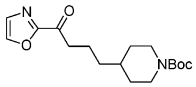
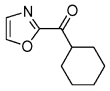
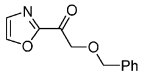
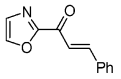
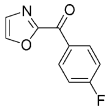
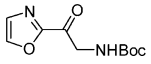
(13) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Adler, M.; Adler, S.; Boche, G. *J. Phys Org. Chem.* **2005**, *18*, 193−209. (c) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340−347.

(14) Reactions between 5-phenyl-2-lithiooxazole and *N*-methyl-*N*-(2-pyridinyl)carboxamides have been previously documented to provide the desired 2-aroyloxazoles in low yields. Pridgen, L. N.; Shilcrat, S. C. *Synthesis* **1984**, 1048−1050.

(15) Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D., III *Tetrahedron Lett.* **2002**, *43*, 8223−8226.

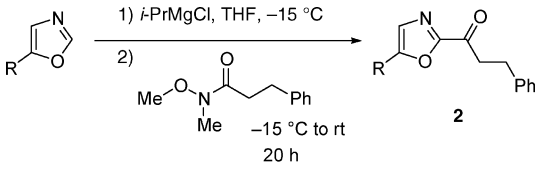
TABLE 1. Reaction between Oxazole Grignard and Various Weinreb Amides

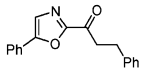
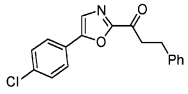
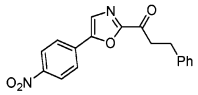
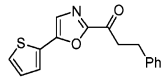
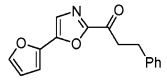
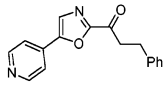
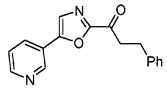
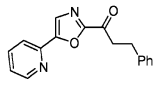


Entry[a]	Product	Yield
1	**1a** 	76%
2	**1b** 	80%
3	**1c** 	77%
4	**1d** 	75%
5	**1e** 	52%
6	**1f** 	74%
7	**1g** 	71%
8	**1h** 	25%

[a] All reactions were run under "standard conditions" as follows: 1.25 equiv of oxazole; 1.25 equiv of *i*-PrMgCl (2 M in THF), 1 equiv of Weinreb amide.

TABLE 2. Reaction between Various Oxazole Grignard Reagents and the Weinreb Amide of Dihydrocinnamic Acid



Entry[a]	Product	Yield
1	**2a** 	48%
2	**2b** 	54%
3	**2c** 	-
4	**2d** 	40%
5	**2e** 	60%
6	**2f** 	79%
7	**2g** 	60%
8	**2h** 	-

[a] All reactions were run under "standard conditions" as follows: 1.25 equiv of oxazole; 1.25 equiv of *i*-PrMgCl (2 M in THF), 1 equiv of Weinreb amide.

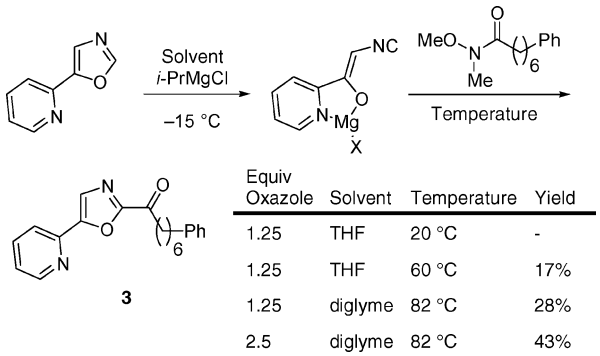
In most cases, these reactions are extraordinarily clean with mass balances consisting of predominantly unreacted starting materials.

Finally, we were interested in determining whether this methodology could be applied to a series of 5-aryl and 5-heteroaryl oxazoles (Table 2). In the case of simple aryl oxazoles, moderate yields were obtained with 5-phenyl and 5-(*p*-chlorophenyl) variants (entries 1 and 2). With 5-(*p*-nitrophenyl) (entry 3), the reaction gave rise to a number of byproducts including the vicarious nucleophilic substitution product; however, no desired product was recovered. Both 5-(thiophen-2-yl) and 5-(furan-2-yl) oxazoles provided products in moderate to good yields (entries 4 and 5). Interestingly, through the series of 5-pyridinyl oxazoles, the substitution site on the pyridine ring had a drastic effect on the ultimate product yields (entries 6, 7, and 8). The 4-pyridyl system provided the highest yield (79%), with some falloff in the case of the 3-pyridyl system (60%), and no product at all in the case of the 2-pyridyl system.

Since 5-(pyridin-2-yl)-2-acyl oxazoles have shown significant biological activity as fatty acid amide hydrolase inhibitors, we were particularly interested in further pursuit of these targets.[16] Because the reaction under standard conditions provided only starting materials, we reasoned that a higher temperature during

(16) (a) Boger, D. L.; Miyauchi, H.; Du, W.; Hardouin, C.; Fecik, R. A.; Cheng, H.; Hwang, I.; Hedrick, M. P.; Leung, D.; Acevedo, O.; Guimarães, C. R. W.; Jorgensen, W. L.; Cravatt, B. F. *J. Med. Chem.* **2005**, *48*, 1849. (b) Romero, F. A.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 14004−14005.

SCHEME 4. Synthesis of Analogues Arising from Metalation/Addition Reactions of 2-Oxazol-5-ylpyridine



Equiv Oxazole	Solvent	Temperature	Yield
1.25	THF	20 °C	-
1.25	THF	60 °C	17%
1.25	diglyme	82 °C	28%
2.5	diglyme	82 °C	43%

the reaction with the electrophile might prove fruitful. In fact, warming to 60 °C for 2.5 days during reaction with electrophile provided the desired product in 17% isolated yield (Scheme 4).

In an attempt to rationalize the sluggish reaction we hypothesized that the open-chain form of the magnesiated intermediate possessed a heightened stability as a result of potential coordination with the pyridyl nitrogen. To further optimize the reaction, we switched to diglyme as a solvent with a temperature of 82 °C after addition of the Weinreb amide; these conditions provided the product in a somewhat improved yield of 28%. Most likely, the initially formed tetrahedral intermediate is not stable at 82 °C, and α-keto deprotonation quenches the oxazole Grignard reagent. As a final improvement, increasing the equivalents of oxazole Grignard reagent to 2.5 provides the desired product in a reasonable yield of 43%, with unreacted starting materials providing the majority of the mass balance.

In summary, we have established that oxazole Grignards and Weinreb amides represent a pair of reaction partners that cleanly provide 2-acyl oxazoles in good to high yields. This solves a long-standing problem in the field of oxazole chemistry and provides rapid access to a host of pharmaceutically relevant compounds. The methodology is applicable to both 5-(hetero)-aryl-substituted oxazoles and unsubstituted oxazole. With some fine-tuning it is applicable even to the highly challenging case of 5-(pyridin-2-yl)-2-acyl oxazoles.

Experimental Section

General Procedure for the Synthesis of 2-Acyl Oxazoles from Oxazoles and Weinreb Amides: 4-(4-Oxazol-2-yl-4-oxo-butyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (1c). To a 5-L jacketed reactor equipped with an overhead mechanical stirrer, a thermocouple probe, and a J-Kem dose controller was added THF (1.46 L) under $N_{2(g)}$. After the solution was cooled to an internal temperature of −15 °C, oxazole (25.60 g, 371 mmol, 1.2 equiv) was added and the dose controller was utilized to meter in *i*-PrMgCl (2 M in THF, 186 mL, 371 mmol, 1.2 equiv) over 20 min, maintaining an internal temperature of <−10 °C. The homogeneous solution was then stirred for 40 min. After this aging period, 4-[3-(methoxymethylcarbamoyl)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (S3) (97.25 g, 309 mmol, 1.0 equiv) was added in 550 mL of THF over 8 min maintaining an internal temperature below −14 °C. The reaction was then warmed to a jacket temperature of 28 °C and stirred for 13 h. After this hold time, the reaction was quenched by addition of 13.5% $NH_4Cl_{(aq)}$ w/w (2 L). The layers were mixed and then separated and the aqueous layer was extracted once with MTBE (1.5 L). The combined organics were dried over $MgSO_4$, filtered, and concentrated to a crude mass of 110.74 g. The material was purified through filtration through a plug of silica gel with 25% EA/hexanes to provide the desired product **1c** as a white solid (76.91 g, 77%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.84 (s, 1H), 7.34 (s, 1H), 4.25−3.90 (br s, 2H), 3.07 (t, J = 7.4, 2H), 2.81−2.55 (br s, 2H), 1.81−1.75 (m, 2H), 1.67 (br d, J = 12.7, 2H), 1.47−1.39 (m, 1H), 1.45 (br s, 9H), 1.36−1.30 (m, 2H), 1.09 (qd, J = 12.6, 4.1, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 188.3, 158.0, 154.8, 141.6, 129.0, 79.2, 39.2, 35.85, 35.78, 32.0, 28.4, 20.9. Anal. Calcd for $C_{17}H_{26}N_2O_4$: C 63.33, H 8.13, N 8.69. Found: C 63.43, H 7.83, N 8.91.

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Supporting Information Available: Experimental and spectral details for compounds **1a**−**h**, **2a**,**b**,**d**−**g**, and **3**, as well as for starting Weinreb amides and oxazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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