

Weinreb Amides

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Published online: 05.02.2015

DOI: 10.1055/s-0034-1380055; Art ID: st-2014-v0506-v

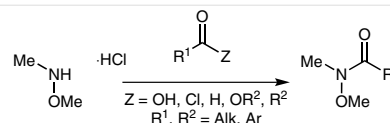
Monika Nowak was born in Międzybrodzie Bialskie, Poland in 1986. She graduated from the University of Łódź in 2012 and received her M.Sc. Currently, she works under the supervision of Prof. Dr. Andrzej Józwiak and Dr. Zbigniew Malinowski. Her research interests focus on metal-catalysed coupling reactions and their applications for the synthesis of new bioactive derivatives of benzoquinazolinone and benzoquinoline.



Introduction

N-Methoxy-*N*-methylamides (Weinreb amides, WA) discovered by Weinreb and co-worker¹ can be prepared from easy available *N,O*-dimethylhydroxylamine hydrochloride (MeNHOMe·HCl) with for example: carboxylic acids, acid chlorides, esters, aldehydes, ketones (Scheme 1).² These amides are interesting building blocks in synthetic chemis-

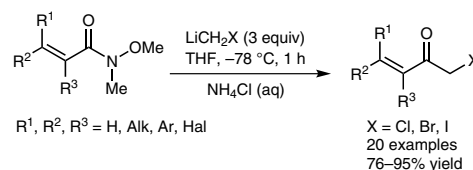
try. They are used to synthesize ketones, aldehydes or cyclic compounds by Grignard reaction, organolithium addition, reduction or acylation reaction of various compounds.^{3–12}



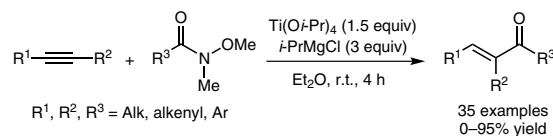
Scheme 1

Table 1 Use of Weinreb Amides

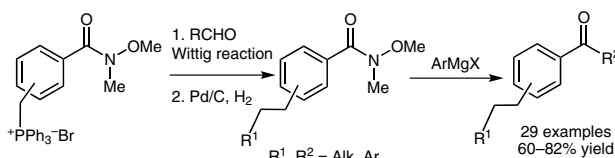
(A) Pace et al.³ described a simple and efficient method for the synthesis of α,β -unsaturated α' -haloketones from Weinreb amides and halomethyl lithium carbenoids, generated in situ from dihalomethane and MeLi–LiBr.



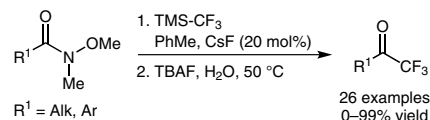
(B) Silwal and Rahaim⁴ reported a Ti-promoted coupling protocol for the synthesis of *E*-substituted enones with high regioselectivity and moderate chemoselectivity from Weinreb amides and unsymmetrical alkynes.



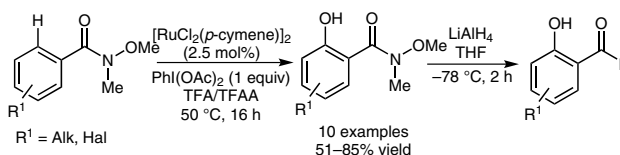
(C) Sivaraman and Aidhen⁵ showed that Weinreb amides can be functionalized through nucleophilic addition in a Wittig reaction and reaction with Grignard reagents. It is a powerful method of constructing unsymmetrical diaryl ketones and constitutes a synthetic route to obtain compounds with biological activities, for example phenastatin analogues.



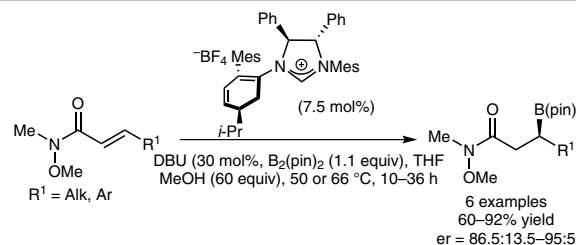
(D) N. E. Leadbeater et al.⁶ presented a new effective method for the preparation of trifluoromethylketones (TFMKs). Trifluoromethylation of aliphatic or heterocyclic Weinreb amides using the Ruppert–Prakash reagent (TMS–CF₃) provided good to very good yields (except *o*-substituted WA). Under trifluoromethylation reaction conditions the α,β -unsaturated WA were also explored but low yields of TFMK were obtained.



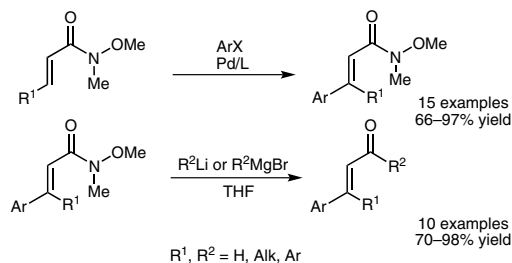
(E) Yang and Ackermann⁷ discovered an economical method of obtaining *ortho*-hydroxy benzaldehydes via direct C–H bond oxygenation of aryl Weinreb amides. Thus, *ortho*-hydroxylated Weinreb amides received from a Ru-catalysed protocol can then under reductive conditions be easily converted into the corresponding aldehydes in good yield.



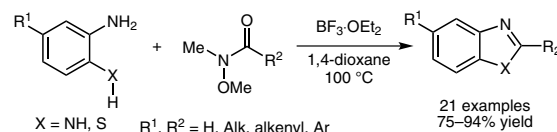
(F) Hoveyda and co-workers⁸ showed metal-free transformation of unsaturated Weinreb amides to β -boryl Weinreb amides. The C–B bond-forming process occurred in the presence of diastereo- and enantiomerically pure N-heterocyclic carbenes (NHC) that were generated in situ. The addition reactions of bis(pinacolato)diboron $[B_2(\text{pin})_2]$ led to β -boryl products in good yield.



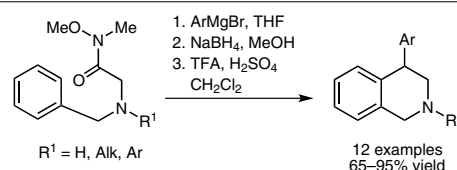
(G) Donohoe and co-workers⁹ reported that unsaturated Weinreb amides underwent Heck reaction with aryl halogens. The use of Weinreb amides in C–C coupling is a great alternative to vinyl ketones. The WA can be selectively changed in different unsaturated regions of the molecule, in Heck reaction or reaction with organometallic reagents, respectively.



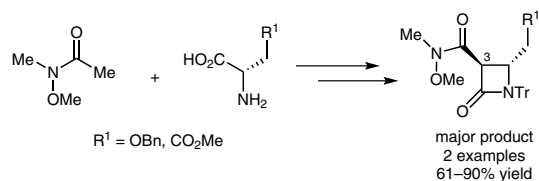
(H) Rangappa, Sadashiva and co-workers¹⁰ observed that Weinreb amides containing carboxyl, halogen, cyano, and methoxy groups, can be easily converted into 2-substituted benzimidazoles and benzothiazoles, in a one-pot cyclization reaction in the presence of $BF_3 \cdot OEt_2$.



(I) Aidhen and co-workers¹¹ showed a new synthetic route for the preparation of various 4-aryl-1,2,3,4-tetrahydroisoquinolines. The protocol is based on the reaction of Weinreb amides with arylmagnesium halide, then reduction and acid-promoted cyclization reaction follow.



(J) J. P. Konopelski et al.¹² showed an efficient method for the synthesis of enantiomerically pure β -lactams from α -amino acids and Weinreb amides as control elements on the C3 position, under photolysis condition reactions (via Wolff rearrangement).



References

- Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, 22, 3815.
- (a) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, 342, 340. (b) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203. (c) List, B.; Castello, C. *Synlett* **2001**, 1687.
- Pace, V.; Castoldi, L.; Holzer, W. *J. Org. Chem.* **2013**, 78, 7764.
- Silwal, S.; Rahaim, R. J. *J. Org. Chem.* **2014**, 79, 8469.
- Sivaraman, B.; Aidhen, I. S. *Eur. J. Org. Chem.* **2010**, 4991.
- Rudzinski, D. A.; Kelly, B.; Leadbeater, N. E. *Chem. Commun.* **2012**, 48, 9610.
- Yang, F.; Ackermann, L. *Org. Lett.* **2013**, 15, 718.
- Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, 134, 8277.
- Baker, D. B.; Gallagher, P. T.; Donohoe, T. J. *Tetrahedron* **2013**, 69, 3690.
- Bommegowda, Y. K.; Lingaraju, G. S.; Thamas, S.; Kumar, K. S. V.; Kumara, Ch. S. P.; Rangappa, K. S.; Sadashiva, M. P. *Tetrahedron Lett.* **2013**, 54, 2693; and references cited therein.
- Kommidi, H.; Balasubramaniam, S.; Aidhen, I. S. *Tetrahedron* **2010**, 66, 3723.
- Vaske, Y. S. M.; Mahoney, M. E.; Konopelski, J. P.; Rogow, D. L.; McDonald, W. J. *Am. Chem. Soc.* **2010**, 132, 11379.