Synthesis of Weinreb and their Derivatives (A-Review)

MAHER KHALID*, SHIREEN MOHAMMED and AMIN KALO

Department of Chemistry, Faculty of Science, Zakho University, Duhok street, 42002 Kurdistan–Region, Iraq.
*Corresponding author E-mail: maher-333@hotmail.de

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ABSTRACT

Due to the largely and an efficient usage of Weinreb amides or N-methoxy-N-methylamides as are remarkable intermediate in the organic synthesis field, the recent review paper provides a considerable development literature survey on the Weinreb amides synthesis. The direct transformation of carboxylic acids, acid chlorides, and esters to aldehydes or ketones employing organometallic reagents do not lead in high yields, since the high reactivity of ketone intermediates toward the organometallic reagents. While, the conversion to the appropriate Weinreb Amides, followed by treatment with the organometallic regent, result the stable expected ketones as the stable initial adduct toward further reactions. Furthermore, Weinreb amides undergo nucleophilic addition and produce a unique and steady five-membered cyclic intermediate which protects the over-addition, leading to a serious transformation.

Keywords: Weinreb amides, Weinreb benzamide, Organometallic reagents, \( \beta \)-trifluoromethylated enaminones, \( \alpha \)-amino aldehydes.

INTRODUCTION

N-methoxy-N-methylamides or Weinreb amides become a worthy synthetic precursor in organic synthesis. The first synthesis of Weinreb moiety was reported in 1981 which performed via...
treatment of N,O-dimethyl hydroxylamine with AlMe₃ as a coupling reagent. Thereafter, several methods for Weinreb amide synthesis have been reported, like direct transformation of carboxyl group into the corresponding aldehyde or ketone. Exceptionally, the efficiency of Weinreb structure to subject a unique substitution reaction with excess of organometallic reagents in the laboratory and industrial synthesis processes. Weinreb structure reacts closely with organolithium, Grignard reagents, LiAlH₄ and Wittig reagents to produce aldehydes or ketones. Currently, much effort has been devoted to develop their soft and universal synthesis. Such, Weinreb amides can be synthesized from carboxylic acids, acid chlorides, amides, esters, lactones and anhydrides. Due to the fast evolution of Weinreb amides synthesis and their applications in the last twenty years, it was interesting to review commonly issue papers in the duration from 2001 to 2009 and detail several neoteric developments of these strategy processes.

In 2001, Giacomelli and co-workers described a flexible process for the synthesis of hydroxamates, Weinreb amides and hydroxamic acids (Scheme 1). The procedure is used coupling agents like triazine derivatives, carboxylic acids and N-protected amino acids as reactants for preparation of N-methoxy-N-methyl amides (Weinreb amides). However, the organic compound like hydroxamic acids can be formed from the transformation of hydroxamates and Weinreb amides as O-benzyl and O-silyl hydroxamates. In addition, handling of reactant for example carboxylic acid 1 with 2-chloro-4,6-dimethoxy-triazine (CDMT) and N-methylmorpholine (NMM) in THF. Subsequently, treatment with N,O-dimethylhydroxylamine yields the desired N-methoxy-N-methylamide products (Weinreb amide and O-benzyl- or tert-butyldiphenylsilyl hydroxylamine for hydroxamates).

While, Fehrentz and co-workers detailed a facile synthesis of lipopeptides via using Weinreb (N-methoxy,N-methyl) amide as an aldehyde function precursor on the side chains of Asp or Glu residues (Scheme 2). The reducing of amide 5 by LiAlH₄ produce the reactive aldehyde function 6. Subsequently, the latter can undergo reaction with yilde 7 to form unsaturated or saturated side 8 chains or with various nucleophiles to yield non-coded amino acid residues incorporated into the sequence. Lastly, racemization by enol formation cannot take place when aldehyde function is formed in position of γ or δ. This condition is not like form of α-amino aldehydes.

Scheme 2. Synthesis of model peptides and incorporation of the alkyl side chains
In parallel, Jeong group reported a novel approach to the synthesis of β-trifluoromethyl enamines with good yields (Scheme 3). Here, the protocol focused on the treatment of N-methoxy-N-methylbenzamide (1.0 eq.) with trifluoropropynyl (4.0 eq.) at -78°C with cooling of water and warming to 0°C, followed by quenching with H₂O in the presence of a variety of amines. Furthermore, using of hydrazine or benzamidine as an amine source in this reaction, afforded the expected pyrazole or pyrimidine products.

Furthermore, Lete and co-workers revealed the efficient role of N-(O-iodobenzyl)-pyrrole-2-carboxyamides as internal electrophiles induced proximity effect (CIPE) in Parham-type cyclization reactions, allowing the efficient construction of the indolizinone nucleus (Scheme 4). So, Li-iodine exchange could be selected firstly due to the coordination between organolithium and amide group and secondly the stabilization of the aryllithium moiety. Under reaction condition, Weinreb amides have also been successfully applied as internal electrophiles in cyclization reactions of organo-lithiums educed from alkyliodides and accessing cyclic ketones. Furthermore, this cyclization process, delivered the effective build of the fused pyrrolo[1,2-b]isoquinolines, thieno-[2,3-f] indolizinones, and pyrrolo[1,2-b]acridinones in high yields. This protocol has also been widespread to heteroaryllithiums, allowing a flexible direction to heterocyclic frameworks with prospective pharmacological features that could compete with previously reported strategies.

Independently, Lee and co-worker illustrated the synthesis of various enantiomerically pure 2-acylaziridines from aziridine-2-carboxylate via Weinreb's amide.

In 2004, Fehrentz and co-workers described the synthesis of α-amino aldehydes linked to the support by their amine function (Scheme 6). This method was completed by reduction with LiAlH₄ of the corresponding Weinreb amide linked to the resin. The aldehydes procured were then implicated in Wittig or reductive amination processes. Moreover, the two-step methods, including the conversion of N-protected α-amino acids to the corresponding Weinreb amides then reduction by LiAlH₄, is an effective process for the synthesis of N-protected α-amino aldehyde.
Furthermore, Kunishima and co-workers\textsuperscript{20} illustrated the synthesis of Weinreb amides through the reaction of carboxylic acids with \( N,O \)-dimethylhydroxylamine hydrochloride in the presence of \( 4\)-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) in different solvents such as alcohols and acetonitrile, that can dissolve DMT-MM (Scheme 7). In this context, the preparation of Weinreb amides was done by converting carboxylic acids 24 to the desired Weinreb amide products 26 in higher yields by easily combined with DMT-MM an \( N,O \)-dimethylhydroxylamine hydrochloride substrates 25.

\[ \text{Scheme 7. Preparation of Weinreb Amides Using (DMT-MM)} \]

Moreover, Franck and co-workers\textsuperscript{22} examined the cycloaddition of Weinreb amide bearing nitrile oxide/nitrones functional groups with a scope of dipolarophiles (Scheme 9). However, there are two synthetic route options for the synthesis of Weinreb amide nitrile oxide 39 and nitrones 41. Firstly, Weinreb amide nitrile oxide 39 was prepared by reaction of trans-cinnamic acid 31 in two procedures. Cinnamic acids 33 is displayed to ozonolysis to give the expected compound separated as the mixture of aldehyde 33 and its hemiacetal, in methanol as a co-solvent for this process. This mixture of the expected products, anyway, was simply isolated from benzaldehyde through flash chromatography. Handling of aldehyde 34 with hydroxylamine hydrochloride 35 gave with quantitative yield of the crude Weinreb amide-oxime 36. The latter 38 can be transformed to nitrile oxide 39 through the classical chlorination method in the presence of NCS\textsubscript{37} then elimination of HCl usesEt\textsubscript{3}N (Synthetic Option 1). Subsequently, the Weinreb amide-nitrene 41 was prepared by reaction between Weinreb aldehyde 34 and \( N \)-benzyl hydroxylamine hydrochloride 40. The crude nitrene 41 was directly used in the cycloaddition process without additional purification (Synthetic Option 2).

While Dake and co-workers\textsuperscript{23} described an appropriate strategy for the transformation of bulky carboxylic acids 42 to \( N \)-methoxy-\( N \)-methylamides 45. Therefore, this transformation can be efficiently completed with \( N \)-methanesulfonyl chloride
43 (1.1 eq.), triethylamine (3 eq.), and N-methoxy-N-methylamine 44 (1.1 eq.) (Scheme 10). The percentage yields for this process range were up to 88%. Remarkable, removal of, N-methoxy-N-methylmethanesulfonamide as the major byproduct in such reactions, was done by set it under vacuum for overnight. Furthermore, this process was necessary for dissolving their individual synthetic problem, and could demonstrate valuable for other practitioners of organic chemistry.

Scheme 9. Preparation of Weinreb Amide-Nitrile Oxide and Weinreb Amide Nitrones.

Synthetic Option 1:

Scheme 10. Formation of Hindered Weinreb Amides.

In 2005, Lee and co-workers provided a novel preparation of N-methoxy-N-methylamides through the reaction of S-2-Pyridyl Thiocarbamate with Grignard reagents (Scheme 11). The authors suggested to prepare N-methoxy-N-methylamides 50 in the convenience of one step operation, and also can be recently made through the reaction of S-2-pyridyl Thiocarbamate 48 with Grignard reagents 49 under mild conditions. Subsequently, preparation of S-2-Pyridyl Thiocarbamate 48 through reaction of N,O-dimethylhydroxylamine hydrochloride 47 with S,S-di(2-pyridyl) dithiocarbonate 46 in the presence of triethylamine in DCM at 0°C. However, the successful synthesis of N-methoxy-N-methylamides 50 using S-2-PyridylThiocarbamate relies broadly on the selective of 2-thiopyridyl group in the substitution reaction.

Scheme 11. Synthesis of N-Methoxy-N-methylamides form S-2-Pyridyl Thiocarbamate and Grignard Reagents

R = CH₃(CH₂)₇, c-C₆H₁₁, C₆H₅ −C≡C, C₆H₅, α-CH₃-C₆H₄, α-CH₃-C₆H₄, p-CH₃-C₆H₄, p-CH₃-O-C₆H₄, p-Cl-C₆H₄, α-Naphthyl, 2-Thienyl
Later, Davis and co-workers reported an innovative strategy for the preparation of N-Sulfinyl-β-Amino carbonyl compounds (Scheme 12). Here, an inclusive methodology protocol has been submitted by the addition of the potassium enolate of N-methoxy-N-methylacetamide 52 to sulfinimines 51 or by handling N-sulfinyl β-amino esters 53 with lithium N,O-dimethylhydroxyamine 54, producing related N-sulfinyl β-amino Weinreb amide products with high diastereoselectivity. This new method reveals as a common solution to the problem of β-amino carbonyl compounds synthesis, via reaction with different organometallic compounds which are significantly moieties and ingredients of natural products. Additionally, this methodology performed a universal solution to the matter of β-amino carbonyl syntheses, which are remarkable chiral frameworks and components of natural products.

Murphy and co-workers demonstrated the direct transformation of Weinreb Amides (N-methoxy-N-methylamides) to the related ketones through unusual Wittig reaction (Scheme 13). Moreover, this reaction proceeds through treatment of N-methoxy-N-methylamides 58 with alkylidenetriphenylphosphoranes 59, followed by one-pot hydrolysis of the intermediate to produce the corresponding ketone products 60. Furthermore, this conversion takes place in a way which prevents the high reactivity of organometallic reagents. Finally, the reaction conditions were considerably reasonable than the transformation route in the presence of organometallic reagents. In addition, its chemoselectivity is mostly observed in the pure conversions of cyano- or halo-substituted substrates.

Moreover, Conrad and co-workers revealed an effective one-pot method for α-amino ketone synthesis through the arylation of Weinreb amides whereas retaining chirality of the main amide (Scheme 14). Actually, this reaction improved quietness when i-PrMgCl (2.5 eq.) was straightway added into the solution of Weinreb amide 61 and 3,5-bis (trifluoromethyl) bromobenzene 62 at 10°C. The method, distinctly proves that the Knochel magnesiztions are kinetically going slower than deprotonating comparing to organolithium transmetallations.

In 2006, Pelkey and co-workers have reported a functional synthetic path to 3,4-disubstituted pyrrole-2-carboxaldehydes and 3-pyrrolin-2-ones starting from Pyrrole Weinreb Amides (Scheme 15). Here, a region-controlled preparation of 3,4-disubstituted pyrrole-2-carboxaldehydes was achieved over two main steps using acyclic substrates. (i) Barton-Zard pyrrole method through reaction between N-methoxy-N-
methyl-2-isocyanoacetamide 66 and β-nitroacetates 64 or α-nitroalkenes 65, providing pyrrole Weinreb amides 67; (ii) reduction reaction step of pyrrole-2-carboxaldehydes 68; and (iii) the regioselective oxidation step of 3-pyrrolin-2-ones 69. Remarkably, this method licensed to the preparation of non-synmetrical pyrrole-2-carboxaldehydes 68 and 3-pyrrolin-2-ones 69 with estimate to substituent'sexisting in the α-positions, and this could demonstrate helpful for the synthesis of oligopyrrole compounds.

Scheme 15. Synthesis of Pyrrole-2-carboxaldehydes and 3-Pyrrolin-2-ones from Pyrrole Weinreb Amides

In parallel John A. Murphy and co-workers described the efficient transformation of Weinreb amides of formic acid to aldehyde products 72 under Wittig reaction conditions (Scheme 16). Under the optimal reaction conditions, treatment of phosphorus on the Weinreb amide of formic acid 70 with organometallics like organolithium or Grignard reagents 69. The qualification of this method is imputed to the stability of tetrahedral intermediate, that does not undergo fragmentation to the expected aldehyde product 72 until work-up.

Scheme 16. Preparation of Aldehyde via Wittig Reaction

Furthermore, Buchwald and co-workers developed the efficient protocol for the synthesis of Weinreb amides through Pd-catalyzed aminocarbonylation of aryl bromide substrates at atmospheric pressure(Scheme 17). The reaction is the transformation of aryl bromides 73 to the corresponding Weinreb amide products 76 under 1 atm of CO 75 and catalytic conditions. A wide range of functional groups, including electron-deficient, -neutral, and -rich aryl bromides 72 were tested and shown their effectiveness transformation to the desired products 76.

Meanwhile, Collum and co-workers described acylation mechanism of Weinreb amide with Lithium phenylacetylide (Scheme 18). The protocol here described the reaction of dimeric lithium acetylide via a mono solvated monomer-based transition structure. The sturdy tetrahedral intermediate stylesconsecutive a C1 2:2 mixed tetramer in the presence of excess lithium acetylide 78 and a 1:3 (alkoxide-rich) mixed tetramer. The stabilization of the mixed tetramers iscompatible with a declared auto inhibition. In addition, the tetrahedral intermediate reacts with lithium phenylacetylide (PhCCLi) 78 in the presence of Weinreb amide 77as a reagent to form ketone compound derivative 79.
Independently, John Nielsen and co-workers\textsuperscript{32} detailed the preparation of \((E)-N\)-methoxy-\(N\)-methyl-\(\beta\)-enaminoketoesters and also novel synthetic pioneers for the region-selective synthesis of heterocyclics (Scheme 19). First, Weinreb amides \(81\) react with the Li- or Na- acetylide of ethyl propynoate \(80\) in a hitherto acyl substitution−conjugate addition series to produce \((E)-N\)-methoxy-\(N\)-methyl-\(\beta\)-enaminoketoesters \(82\), second, this protocol affords a variety access to violently functionalized heterocyclics, inclusive pyrazoles \(84\) through region-selective cyclo-condensations with hydrazine compounds \(83\) applying microwave-assisted reaction.

In 2007, Davis and co-workers\textsuperscript{33} reported the asymmetric preparation of \textit{syn-}\(\alpha\)-substituted \(\beta\)-amino acid through a reaction of pro-chiral lithium enolates of Weinreb amides and sulfinimines (\(N\)-sulfinyl imines) (Scheme 20). The protocol here first focused on the reaction of sulfinimine-derived \(\alpha\)-substituted \(\beta\)-amino Weinreb amide with organometallic compounds. While the direct synthesis of major \(\alpha\)-substituted \(\beta\)-amino Weinreb amide products \(87\) proceeded through the addition of a prochiral Weinreb amide enolate \(86\) to a sulfinimine \(85\). Moreover, the sulfinimine-derived chiral building blocks are considered as significant pioneers of \textit{syn-}\(\alpha\)-substituted \(\beta\)-amino acid derivatives, through hydrolysis, reduction, and reaction with Grignard reagents, individually.

Though, Kim and co-workers\textsuperscript{34} suggested a novel and effective procedure for the transformation of different carboxylic acids to their analogical Weinreb amides employing triphosgene as an acid activator (Scheme 21). This reaction encompasses the treatment of carboxylic acid \(89\) with triphosgene \(90\) to give an acid chloride or anhydride, followed by handling with \(N,O\)-dimethylhydroxylamine \(91\) to produce the expected Weinreb amide \(92\). The current method afforded high yields, short reaction time, and workable accessibility.

While, Jeong and his group\textsuperscript{35} reported dynamic one-pot preparation of unusual \(\alpha\), \(\beta\)-dichloro-\(\beta\)-trifluoromethylated enones (Scheme 22). The stages of protocol start with the reaction of Weinreb benzamides \(94\) and trifluoropropynyllithium \(93\) in THF at -78 to 0°C, followed by handling with trifluoromethanesulfonyl chloride \(95\) to produce \(\alpha\), \(\beta\)-dichloro-\(\beta\)-trifluoromethylated enones \(96\) in moderate yields. While the reaction of \(\alpha\), \(\beta\)-dichloro-\(\beta\)-trifluoromethylated enones \(96\) with substitute amidines \(98\) or hydrazinereagents \(102\) in reflux mixture of 1,4-dioxane/\(\text{CH}_3\text{CN}\) produced trifluoromethylated chloropyrimidines \(99\) and chloropyrazoles \(103\) in acceptable yields. Furthermore, the coupling reactions of trifluoromethylated chloropyrimidines \(99\) with substituted phenylstannane and allylstannane \(100\) in \(\text{CH}_3\text{CN}\) using \(\text{Pd(PPh}_3\text{)}_4\) catalyst under microwave-assisted conditions, provided the desired...
phenyl and allyl substituted pyrimidine products were applied with chloropyrazoles, but did not lead to the product.

Scheme 22. Synthesis of novel \(\alpha,\beta\)-dichloro-\(\beta\)-trifluoromethylated enones and trifluoromethylated heterocycles.

In 2008, Prandi and co-workers\(^3\) described the preparation of newfangled species of heterocyclic Weinreb amides through aminocarbonylation reaction of heterocyclic-derived triflates in the presence of Pd catalyst (Scheme 23). This reaction proceeded through the straightforward conversion of lactone-, thiolactone and lactam-derived triflates into the corresponding morpholine- or \(N\)-methoxy-\(N\)-methyl Weinreb amides. The protocol here suggested to proceed through using CO 75 under mild conditions. However, the amides steadily reacted with nucleophiles to yield the desired heterocycle products. This new protocol discloses the outlet to important dynamically heterocyclic scopes that are favorable as building blocks in total syntheses, and the suggested methodology could be convenient profit for the dienone synthesis, as helpful moieties for Nazarov cyclization.

Scheme 23. Synthesis of Weinreb Amides via Pd-Catalyzed Aminocarbonylation of Heterocyclic-Derived Triflates.

Next, Somfai and co-workers\(^3\) reported an efficient and diastereoselective synthesis of aryl glycines from Weinreb amides employing \(\alpha\)-arylation process (Scheme 24). In such reaction, a novel \(\alpha\)-arylation reaction proceeds smoothly through the reaction between amides electrophile and aryl Grignard reagents as nucleophile in the presence of LDA as a base in THF at low temperature. The mechanism of this reaction starts with deprotonating and the generation of enolate, followed by elimination of tBuO. While the nucleophilic addition of the Grignard reagent to form amide.

Scheme 24. Synthesis of Aryl Glycines by the \(\alpha\) Arylation of Weinreb Amides.
Recently, Li and co-workers\(^3\), described the synthesis of diverse chiral \(N\)-phosphonyl \(\beta\)-amino Weinreb amides 115 via reaction of chiral \(N\)-phosphonyl imines 113 with the lithium enolate of \(N\)-methoxy-\(N\)-methylacetamide 114 employing mild conditions (Scheme 25). Generally, the deprotonation base and presence of protection groups on chiral \(N\)-phosphonyl imines were the pivotal success of such reactions. Commonly, \(N\)-phosphonyl imines uses as electrophiles 113 for some nucleophilic addition reactions, like aza-Darzens, aza-Henry reaction, and allylmagnesium bromide based addition, various wide of Weinreb amides were prepared in excellent yields (up to 98%) with high diastereoselectivities. Furthermore, the ultimate structures were uniquely specified by the transformation the products into original samples and equal their optical rotation assessments.

Meanwhile, Huet et al.\(^3\) reported a wonderful reagent, \(\text{P[NCH}_3(\text{OCH}_3)}\)\(_3\), for the direct synthesis of Weinreb amides 120 from carboxylic acids 119 (Scheme 26). So firstly, treatment \(N,O\)-dimethylhydroxylaminehydrochloride 116 with \(\text{PCl}_3\) in \(\text{Et}_2\text{O}\) uses triethylamine as a base to give \(\text{P[NCH}_3(\text{OCH}_3)}\)\(_3\) in 67% yield. Secondly, \(\text{P[NCH}_3(\text{OCH}_3)}\)\(_3\) can be utilized for the conversion of various kinds of carboxylic acids included aliphatic, aromatic, sterically hindered, and dioic acids in toluene into the expected Weinrebamide products in excellent yields employing soft conditions.

**CONCLUSION**

Newly, assorted investigations have itemized the utilization of Weinreb amide developments as an awesome intermediate in natural blend reaction. In this sheet, we displayed this side of the written works, including an abnormal preparation of Weinreb amides and their employments by explaining convention instances of these procedures. Besides, this paper contains a definitive finish of the specialists and conveniently outfits reaction data for the exceedingly significant reaction and numerous indications to the regional literature.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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