Weinreb amide based building blocks for convenient access to various synthetic targets

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N-Methoxy-N-methylamide, popularly known as the Weinreb amide (WA), has served as an excellent acylating agent for organolithium and/or organomagnesium reagents and a robust equivalent for an aldehyde group. The stability of the WA functionality, its ease of preparation, the scalability of its reactions and its predictable reactivity are the key features responsible for its prominent use in several synthetic endeavors by the chemists world-wide. The development of WA-based building blocks and synthetic equivalents for interesting synthons has been a long drawn pursuit initiated in nineties and through this mini-review accomplishments in this direction, with particular emphasis on the building blocks, developed recently in the last three years are summarized.

Keywords: Weinreb amide, building blocks, synthetic equivalent, FTY 720, olefination, sulfone, α-diketones, 4-aryl-tetrahydroisoquinoline

N-Methoxy-N-methylamide 1, popularly addressed as the Weinreb amide, has served as an excellent acylating agent for organolithium or organomagnesium reagents and as a robust equivalent for an aldehyde group. These two aspects have been exploited exhaustively in various synthetic endeavors. Successful acylation by a variety of organolithium and organomagnesium reagents or reductions by lithium aluminum hydride or disobutylaluminum hydride to aldehyde is due to the putative and stable tetrahedral intermediate 2 or 3 formed upon addition of the first equivalent of the organometallic species or reducing agent (Figure 1). This stability precludes the collapse to a ketone or aldehyde under the reaction conditions and thus prevents the formation and subsequent possibility of addition to the ketone or aldehyde. The stability of the WA functionality, its ease of preparation, the scalability of its reactions and its predictable reactivity are the four main reasons for the increasing confidence that synthetic organic chemists have with regard to the use of the WA in various synthetic endeavors.

Concept of WA-based building block from our group during late nineties

Synthesis of new building blocks based upon Weinreb amide functionality a pursuit initiated by us in late nineties has come a long way. In this mini-review, our accomplishments in this direction, with particular emphasis on the building blocks, developed recently in last three years have been summarized. Although the initial developments of these synthetic equivalents were driven by specific objectivity, their use is left to one’s imagination and for any synthetic endeavors. The interest in deoxy-sugars and acyl anion chemistry lead to the idea of synthesizing two WA-based building blocks 4 and 5 (Figure 2). The former was aimed with the purpose of two-carbon homologation of acyclic sugar derivatives and the later for the synthesis of 1,4 diketones through the acyl anion chemistry. The synthetic equivalent 4, N-methoxy-N-methyl-2-phenylsulfonyl-acetamide, developed for two carbon homologation of alkyl halides, can be easily prepared from the reaction of sodium salt of phenylsulfonic acid with α-chloro-N-methoxy-N-methyacacetamide. Reagent 4 undergoes a clean alkylation at the active methylene group with various alkyl halides, especially from the carbohydrate domain under the mild reaction conditions of K_2CO_3 in DMF (Figure 3). Subsequent reductive desulphonylation with sodium amalgam leads to a two carbon homologated product 6. Reduction of the WA functionality in 6 to aldehyde renders the building block 4 equivalent to an acetaldehyde carbanion (synthon A).
This approach of homologating halides through the use of reagent 4, becomes very important because two carbon homologation of aldehydes with α-stereocenters do have a fear of epimerization especially with Wittig based reagents under basic conditions. The two carbon homologation of threo-configured iodide 7 enabled efficient synthesis of 4,5-O-isopropylidene protected L-rhodinose 5, an important trideoxy sugar and that of erythro-configured iodides 8 and 9 have enabled synthesis of another trideoxy sugar, D-amicetose 6. With the use of arabino-configured iodide 10 as the alkylating halide for the 4, it furnished the synthesis of 2,3-dideoxy-4,5:6,7-di-O-isopropylidene-D-arabino-heptose 11, which corresponded to C3-C9 fragment of a natural product (+)-aspicillin 4. The convenient availability of 4 on multigram scale through simple reactions and its successful use in two carbon homologation, afforded itself a place in Aldrich catalogue 7. Although synthetic equivalent 4 could chain extend open-chain primary halides conveniently, it failed to do the same during an attempt to execute C-C bond formation at the anomeric carbon in the pyranosyl iodide 12. This was
probably due to the poor stability of iodide 12 under the reaction conditions (Figure 3).

The genesis of synthetic equivalent 5, N-methoxy-N-methyl-3-bromopropionamide, derived from 3-bromopropionic acid was a result of our interest in the use of α-aminonitriles 13 as acyl anion equivalents. Synthetic equivalent 5, equivalent to synthon B has been applied to the synthesis of two different targets, an unsymmetrical 1,4-diketones 14 (ref. 8) and β-(N,N-disubstituted)amino ketones 15 (ref. 9, Scheme I). Successful alkylation of the carbanion 16 derived from α-aminonitriles 13, an acyl anion equivalent with 5 is the key step. Successful addition of the variety of Grignard reagents onto the alkylated intermediate 17 and unmasking the carbonyl group in the product 18 under acidic hydrolytic conditions paved the way for the synthesis of 1,4-diketones 14. Nucleophilic displacement of bromine in 5 with various secondary amines and subsequent Grignard addition on to β-amino WA 19 furnished the β-amino ketones 15.

Our failure to accomplish the C-C bond formation at the anomeric center using 4, inspired us to explore a strategy similar to the one developed by Kametani et al.10 wherein the phenylthioglycoside 20 had been reacted cleanly with diazo derivative of dimethyl malonate 21 in the presence of rhodium(II) acetate. This lead to the proposal of synthetic equivalent 22 towards the possible accomplishment of the C-C bond formation under the mild and neutral condition using rhodium(II) acetate as a catalyst. The synthetic equivalent 22, a crystalline orange colour solid (m.p. 82-84ºC) could be readily prepared in 72% yield by reacting the sulfone WA 4 with tosyl azide in the presence of DBU as a base11. When synthetic equivalent 22 was reacted with thioglycoside 20, using rhodium (II) acetate as a catalyst at RT in dichloromethane, it was found that thioglycoside 20 remained unreacted and was completely recovered, while the diazo compound 22 was completely consumed (Scheme II). The intermediate of rhodium carbenoid 23 formed under the reaction conditions,
underwent a facile intramolecular C-H insertion at the C-H bond of –OMe group to furnish 24. The product obtained was evident from ¹H NMR data. It showed the presence of three doublet of doublets at δ 4.30, 4.60 and 4.90 for three protons. Also ¹³C NMR, along with DEPT studies showed the presence of methylene carbon at δ 66.4 and methine carbon at δ 67.5 (ref. 11a). To confirm this observation and result, the diazo compound 22 was subjected to the same reaction conditions, but devoid of thioglycoside 20 as a co-reactant. The reaction once again furnished same C-H inserted cyclized product 24 in 67% yield.

New WA-based building block from our group during the recent years (2006-present)

Our failure to accomplish C-C bond formation at the anomeric carbon in pyranoside iodide 12 with building block 4, or with the reaction of diazo compound 22 derived thereof with phenylthioglycoside 20, prompted further search towards alternatives in achieving this objective. Since appending of WA-containing fragment at the anomic position would enable further derivatization, this objective was important, novel and worthy of persuasion. Besides the afore mentioned unaccomplished task, our global objective towards developing novel WA based building blocks for varied synthetic pursuits remained uninterrupted (Figure 4).

The potential and facile possibility of an intramolecular hetero-Michael reaction in the scaffold 25 to furnish not only the C-glucosyl configured pyranoside derivative, but also provide a handle in the form of WA-functionality, lead to the proposal of building block 26. Simultaneously, another clinically important molecule, FTY-720 as an immunosuppressant attracted our attention. The synthesis of this important target through the envisaged disconnection prompted three possible WA-based building blocks, 27, 28 and 29 for the central core of FTY-720.

The synthetic equivalent 26, combines the usefulness of WA-chemistry with Julia olefination protocol. Clean reaction of benzothiazole with α-chloro-N-methoxy-N-methylacetamide followed by oxidation of sulfide to sulfone paved the way for the reagent 26. Successful olefination of aldehydes with the reagent 26, especially from the domain of carbohydrates under NaH in DMF conditions (Scheme III) facilitates the synthesis of α, β-unsaturated WA structural unit 30. This reagent is a viable alternative to the Wittig or HWE methodology for

![Figure 4](image-url)

**Scheme III**
the conversion of aldehydes to α, β-unsaturated N-methoxy-N-methyl amides. This would allow all possible synthetic manipulations associated with α, β unsaturated system and those innate with WA functionality. The synthetic equivalent 26, offers a significant advantage during purification of the products, in contrast to the tedious removal of triphenylphosphine oxide while using the Wittig reaction towards the same objective. In the light of the fact that α, β unsaturated aldehydes and ketones being poor substrates for the asymmetric dihydroxylation (AD) process\(^\text{16}\) and cyclopropanation reaction\(^\text{17}\), the α, β unsaturated N-methoxy-N-methyl amides would allow a great advantage for indirect access to these functionalities. The successful olefination of the gluco-configured aldehyde 31 (ref. 18) resulting in the formation of 32, has paved the way for the synthesis of much desired C-glucoside building 33 (ref. 19) through acid catalyzed terminal isopropylidene removal and subsequent in situ intramolecular Michael reaction.

Synthesis of three bi-functional synthetic equivalents \(\text{27, 28 and 29}\) using commercially available \(p\)-toluic acid was triggered by the importance of FTY-720 as an immunosuppressant (Scheme IV, ref. 20). The polar head group of FTY-720 was incorporated on the central aromatic core presented in these building blocks through Julia, Wittig and HWE reactions by reaction with the requisite aldehyde, \(\text{34}\) (ref. 21). The WA functionality in the olefinated product \(\text{35}\) or further hydrogenated product \(\text{36}\) provided the necessary handle for a complete control at the length of the lipophilic side chain.

All the reactions and conditions en-route to the target molecule are simple and good yielding and therefore hold significant promise in industries. The
olefination of TRIS aldehyde 34 with synthetic equivalents 27 and 28 using 3 equiv of K₂CO₃ in DMF/THF (1:3) mixture at 70°C yielded the product 35 as E-isomer in 70 and 60% yields respectively. The same reaction using Wittig salt 27 afforded the desired product 35 accompanied by its Z-isomer (E/Z= 1:3) in 70% yield. However the simple hydrogenation of E/Z product mixture to compound 36 makes the formation of geometrical isomers inconsequential. The addition of n-C₇H₁₅MgBr on 35 and 36 furnished the ketones 37 and 38 in 70% yields, which on reduction using NaBH₄ and subsequent hydrogenolysis afforded the target compound 39 in good yields. The synthetic equivalent 27 has been applied towards preparing di-ary ketones having highly functionalized appendages and for preparing new analogues of phenstatins, a promising anti-mitotic agent.

The synthetic equivalents N-methoxy-N-methyl-1, 3-dithiolane-2-carboxamide 40 and N-methoxy-N-methyl-1, 3-dithiane-2-carboxamide 41, derived from glyoxalic acid represents α-dicarbonyl unit, synthons C, with opposing polarity. These synthetic equivalents were envisaged for the synthesis of mono-protected α-diketones 42 (Scheme V, ref. 23). Acid catalyzed thietketalization of the aldehyde functionality in glyoxalic acid 43 with 1,2-ethane or 1,3-propane dithiol and later converting the carboxyl group to WA using the mixed anhydride approach yielded the synthetic equivalent 40 and 41 respectively. Nucleophilic addition on to the amide functionality in 40 followed by alkylation at the C₂ position of the dithiolane ring in 44 furnished the targeted mono-protected α-diketones 42.

An interesting application of this new protocol is the successful synthesis of 6-(2-methyl-1,3-dithiolan-2-yl)-2,3,4,5-tetrahydropyridine 45, a dithioacetal protected derivative of an important target molecule 46, a tautomer of a compound responsible for the bread flavour. The requisite carbon skeleton to arrive at compound 45 was easily assembled in good yields by nucleophilic addition of THPO(CH₂)₄MgBr on 40 followed by methylation at C₂ position to furnish 47. Further functional group interconversion allowed convenient access to the azido ketone 48 as a key intermediate which underwent phosphine mediated cyclization affording the target 45 (Scheme VI, ref. 23).

Towards the synthesis of pharmacologically important 4-aryl-1,2,3,4-tetrahydro isoquinoline derivatives 49, two WA-based synthetic equivalents 50 and 51 were envisaged as useful template for the general synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinoline skeleton. Both these synthetic equivalents for the synthon D were easily accessible from glycine in two steps. Although the N-phenylsulfonyl protected, WA-based building block 50 (ref. 26), underwent clean N-benzylation to afford 52 the key intermediate towards the target, our recent studies showed that N-Boc protected analogue 51 (ref. 27) failed to undergo similar N-benzylation in an attempt to arrive at 53 (Figure 5).

Nucleophilic addition of a variety of ArMgX onto WA group in 52 furnished the arylketones 54 which on reduction and acid promoted cyclization afforded the N-sulfonyl protected 4-aryl-1,2,3,4-tetrahydroisoquinoline 55 derivatives. Realizing the convenience of N-Boc removal against N-phenylsulfonyl, in the final step towards the target 49, synthesis of 53 became important. The compound 53 was prepared in three steps using benzylamine and ethyl bromoacetate. The steps involved were mono-alkylation of benzyl amine 56 with ethyl bromoacetate 57,
according to the reported procedure\textsuperscript{28}, followed N-Boc protection with di-tert-butyl carboxy anhydride, ester hydrolysis and in situ conversion of acid to WA through mixed anhydride approach (Scheme VII).

Compound 53 underwent similar set of reactions (53 → 58 → 60) as described for 52, with an additional advantage that during acid promoted cyclization, the N-Boc protection was easily removed. The final 4-aryl-1,2,3,4-tetrahydro isoquinolines 49 were converted to hydrochloride salts for the convenience of isolation (Scheme VIII, ref. 29).

The importance of end-substituted distyrylbenzene (DSB) and their derivatives in electro-optic and solar applications\textsuperscript{30} and as potential energy transporters in one dimensional channel\textsuperscript{31}, we became interested in the synthesis of distyrylbenzene derivative 61a-c with Weinreb amide functionality as one of the end-substituent. Since the modifications in the (a) nature of terminal substituents on the distyrylbenzene scaffold have been found to be very useful and also (b) that the use of Weinreb amide functionality as one of the terminal substituents has never been made, it provided all the basis for the synthesis of compounds 61 as an interesting functional material worthy of investigations in optics (Scheme IX). The DSB derivative containing Weinreb amide functionality, 61a, as a representative example was synthesized by the Julia reaction between the sulfone building block 29 and commercially available terephthaldehyde 62 (ref. 32). This DSB derivative 61a was found to be efficient laser dye than a standard dye (POPOP)\textsuperscript{33} at 518 nm.

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\text{Scheme VII} & \\
\text{Scheme VIII} & \\
\text{Scheme IX}
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the pump wavelength of 355 nm and its third-order optical non linearity is as large as the standard reference molecule carbon disulphide. The synthesis and study of other isomers $61b$ and $61c$ is currently underway.

References
33. POPOP=1,4-di[(5-phenyloxazolyl)]benzene, see: Brackmann U, Lambdachrome Laser Dyes Data Sheets, Lambda Physik, Germany, 1986.