

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 group¹. These two aspects have been exploited exhaustively in various synthetic endeavors². Successful acylation by a variety of organolithium and organomagnesium reagents or reductions by lithium aluminum hydride or diisobutylaluminum 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 endeavors³.

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^{3a}. In this mini-review, our accomplishments in this direction, with particular emphasis on the building blocks, developed recently in last three years have been summarized³. 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 phenylsulfinic acid with α -chloro-*N*-methoxy-*N*-methylacetamide⁴. 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 K₂CO₃ 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**)⁴.

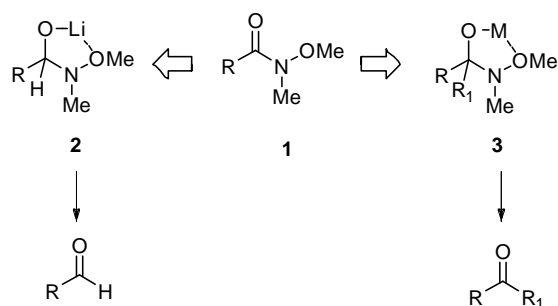


Figure 1

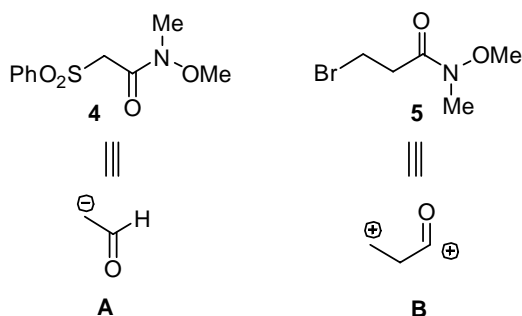


Figure 2

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-rhodinose⁵ an important trideoxy sugar and that of *erythro*-configured iodides **8** and **9** have enabled synthesis of another trideoxy sugar, D-amictose⁶. 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 (+)-aspicillin⁴. The convenient availability of **4** on multi-gram scale through simple reactions and its successful use in two carbon homologation, afforded itself a place in Aldrich catalogue⁷. 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

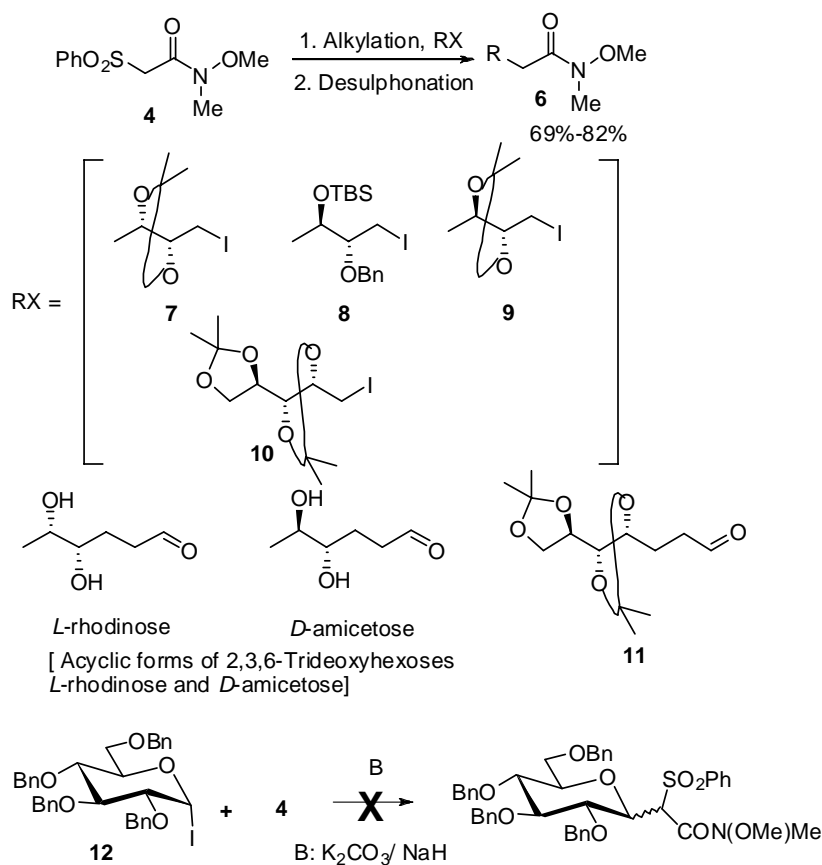
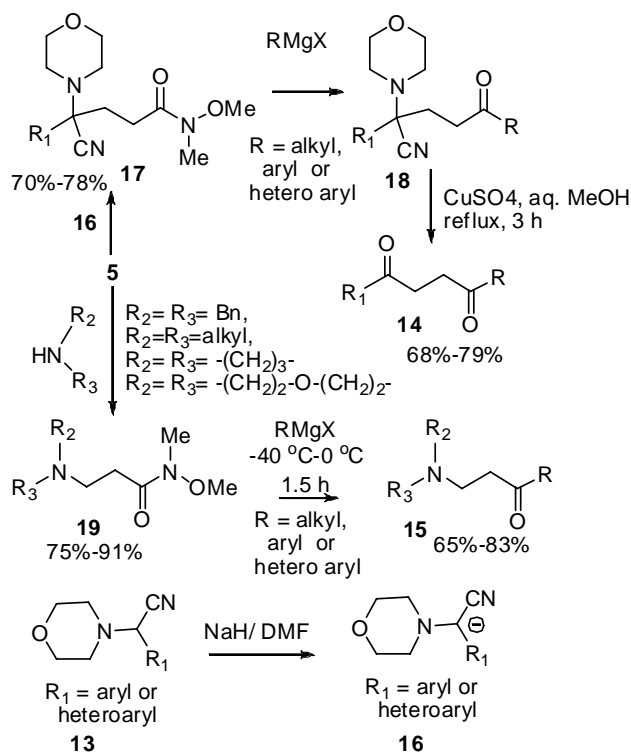


Figure 3

probably due to the poor stability of iodide **12** under the reaction conditions (**Figure 3**).

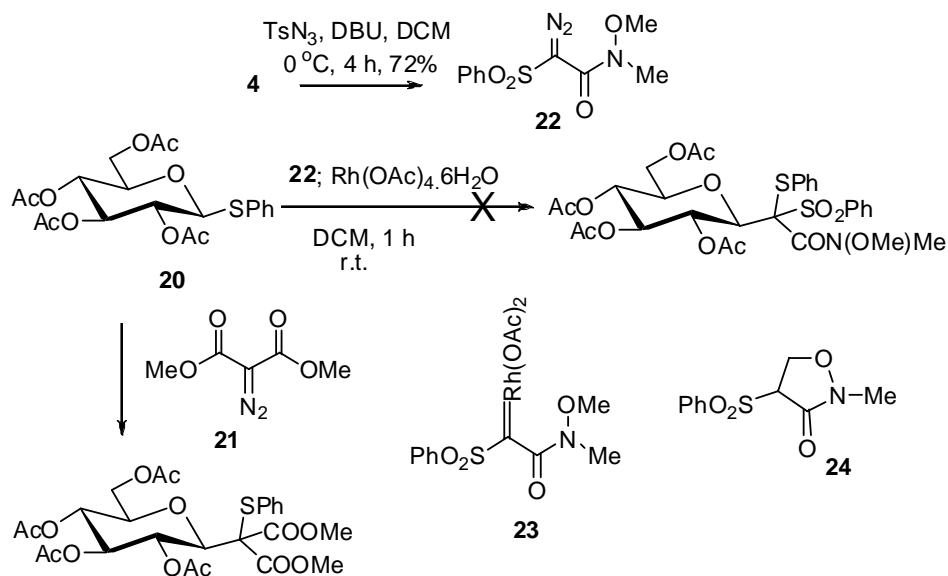
The genesis of synthetic equivalent **5**, *N*-methoxy-*N*-methyl-3-bromopropionamide, derived from 3-bromopropanoic acid was a result of our interest in the use of α -aminonitriles **13** as acyl anion equivalents. Synthetic equivalent **5**, equivalent to synthon **B** has been applied to the synthesis of two different targets, an unsymmetrical 1,4-diketones **14** (ref. 8) and β -(*N*,



Scheme I

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 led 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. 82-84°C) 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,



Scheme II

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 ^{13}C 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

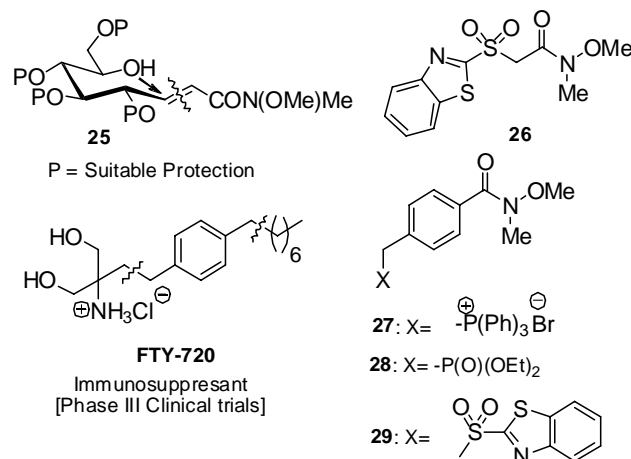
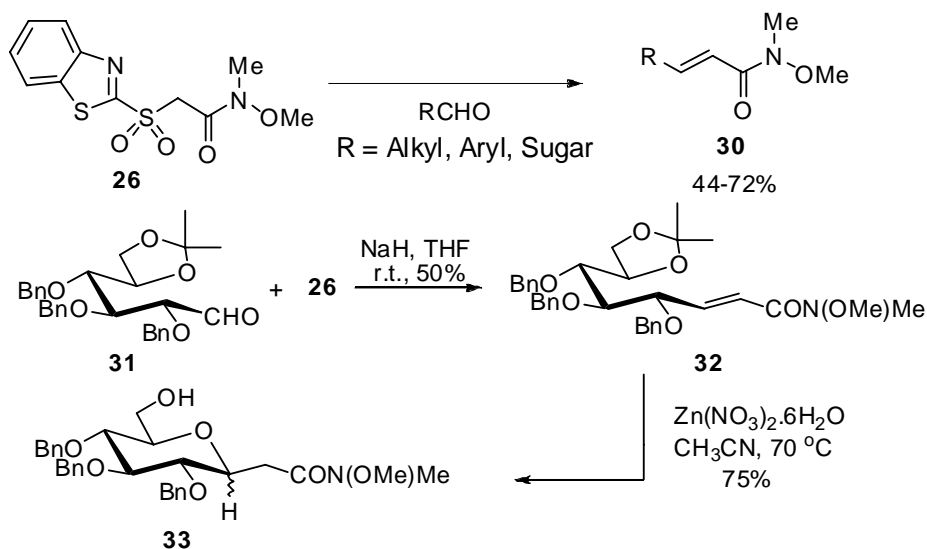


Figure 4

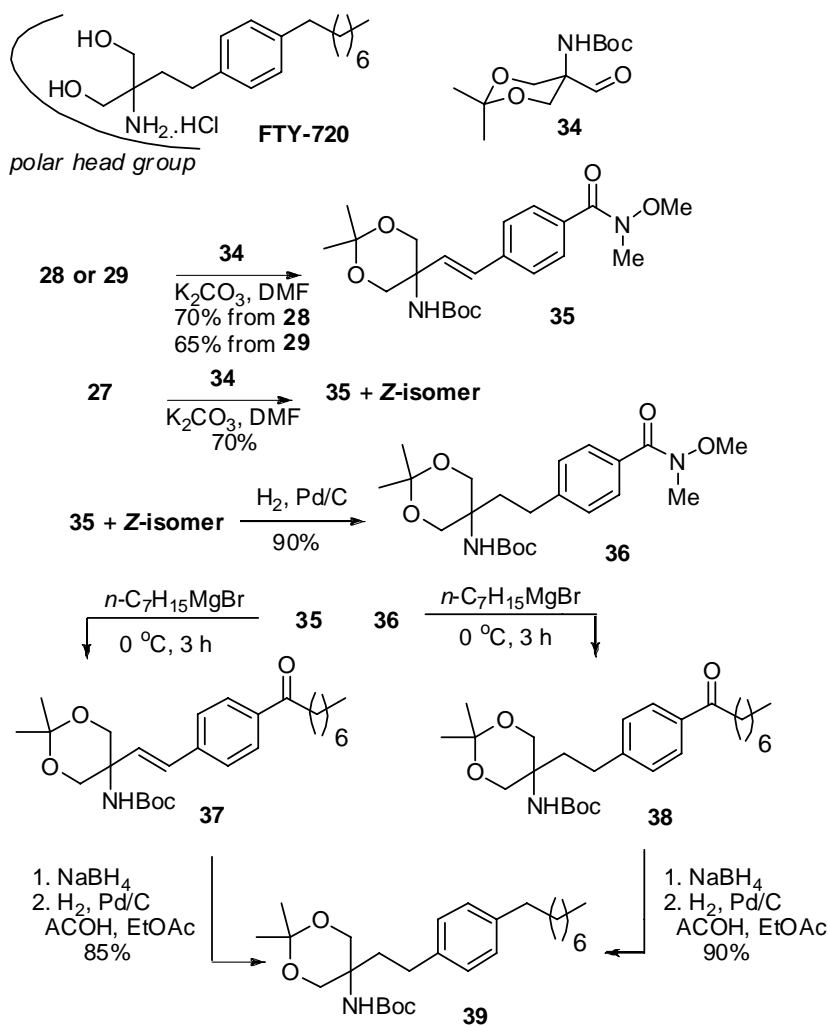
building block **4**, or with the reaction of diazo compound **22** derived thereof with phenylthioglycoside **20**, prompted further search towards alternatives in achieving this objective. Since appending of WA-containing fragment at the anomeric position would enable further derivatization, this objective 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-gluco* 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 immuno-suppressant¹² 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 protocol¹³. 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 Wittig¹⁴ or HWE¹⁵ methodology for



Scheme III



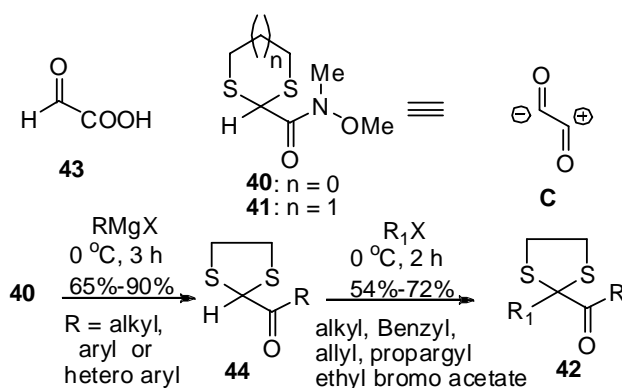
Scheme IV

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) process¹⁶ and cyclopropanation reaction¹⁷, 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

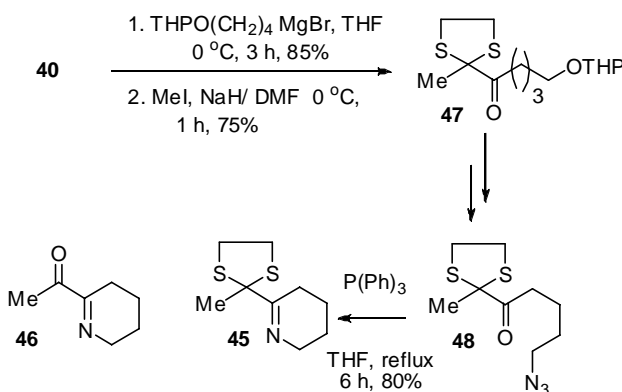
removal and subsequent *in situ* intramolecular Michael reaction.

Synthesis of three bi-functional synthetic equivalents **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, *tert*-butyl 5-formyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate **34** (ref. 21). The WA functionality in the olefinated product **35** or further hydrogenated product **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



Scheme V



Scheme VI

olefination of TRIS aldehyde **34** with synthetic equivalents **27** and **28** using 3 equiv of K_2CO_3 in DMF/THF (1:3) mixture at $70^\circ C$ 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 $n\text{-C}_7\text{H}_{15}\text{MgBr}$ on **35** and **36** furnished the ketones **37** and **38** in 70% yields, which on reduction using NaBH_4 and subsequent hydrogenolysis afforded the target compound **39** in good yields²⁰. The synthetic equivalent **27** has been applied towards preparing di-aryl ketones having highly functionalized appendages and for preparing new analogues of phenstatins, a promising anti mitotic agent²².

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, synthon

C, with opposing polarity. These synthetic equivalents were envisaged for the synthesis of mono-protected α -diketones **42** (Scheme V, ref. 23). Acid catalyzed thioketalization 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 approach²⁴ yielded the synthetic equivalent **40** and **41** respectively. Nucleophilic addition on to the amide functionality in **40** followed by alkylation at the C_2 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 flavour²⁵. The requisite carbon skeleton to arrive at compound **45** was easily assembled in good yields by nucleophilic addition of $\text{THPO}(\text{CH}_2)_4\text{MgBr}$ on **40** followed by methylation at C_2 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).

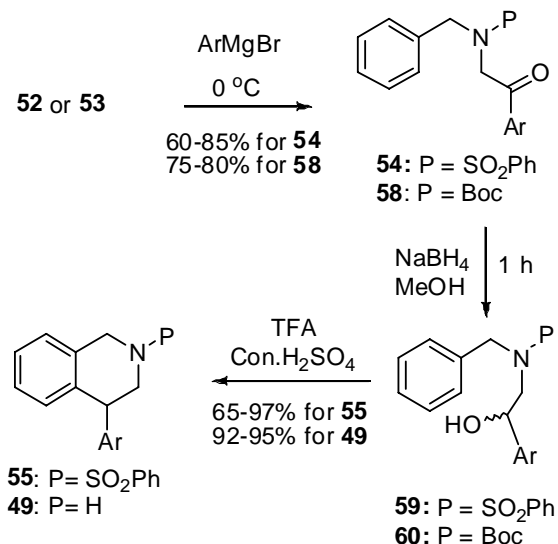
Nucleophilic addition of a variety of ArMgX onto WA group in **52** furnished the arylketones **54** which on reduction and acid promoted cyclization afforded the *N*-sulfonyl protected 4-aryl-1,2,3,4-tetrahydroisoquinoline **55** derivatives²⁶. Realizing the convenience of *N*-Boc removal against *N*-phenylsulfonyl, 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 procedure²⁸, 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 applications³⁰ and as potential energy transporters in one dimensional channel³¹, 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 terephthalaldehyde **62** (ref. 32). This DSB derivative **61a** was found to be efficient laser dye than a standard dye (POPOP)³³ at



Scheme VIII

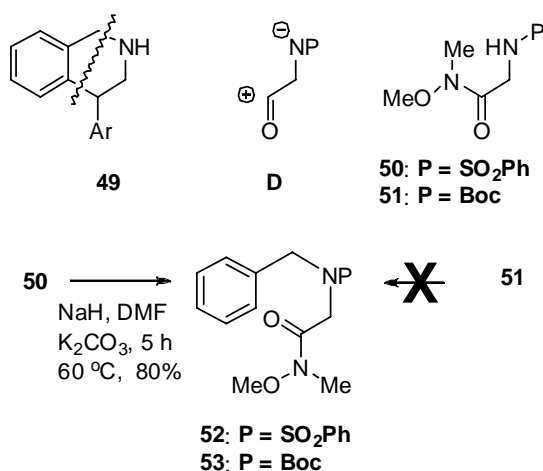
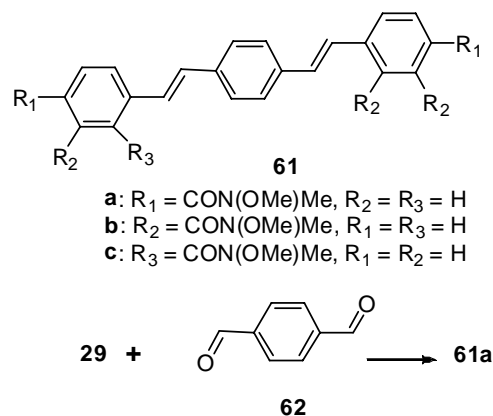
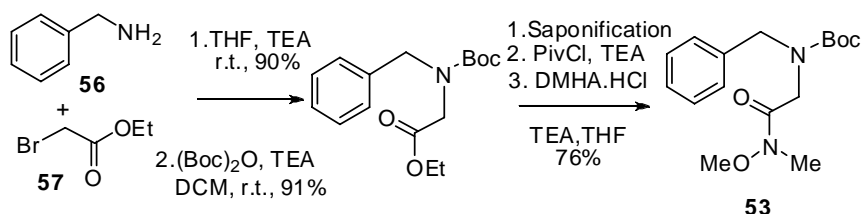


Figure 5



Scheme IX



Scheme VII

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.

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