The Growing Synthetic Utility of Weinreb's Amide

Jaimala Singh*

Chennai (Madras)/India, Division of Organic Chemistry, Central Leather Research Institute

N. Satyamurthi and **Indrapal Singh Aidhen***

Chennai (Madras)/India, Department of Chemistry, Indian Institute of Technology

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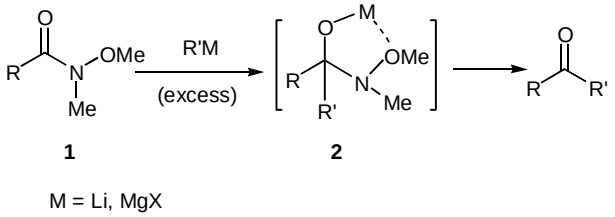
Abstract. The preparation and the synthetic utility of the *N*-methoxy-*N*-methyl amides, also called as Weinreb amides, for the preparation of aldehydes and ketones has been discussed. Also the various reagents based on Weinreb's amide has been compiled.

Since the original discovery of Weinreb [1], that *N*-methoxy-*N*-methyl amides **1**, now popularly called as Weinreb amides (WA), cleanly reacted with Grignard reagents and organolithium to produce ketones, these amides have gained wide importance as very effective acylating agents for various organometallic reagents [2]. Even with large excess of organometallics these amides yield exclusively ketones (Scheme 1). No over addition occurs due to effective chelation of metal ion between carbonyl oxygen and *N*-methoxy oxygen which prevents the collapse of the tetrahedral intermediate **2** until aq acidic work up.



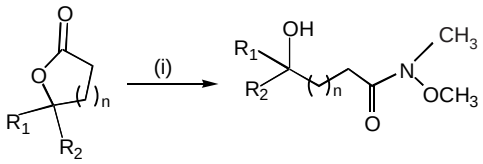
1 **2**

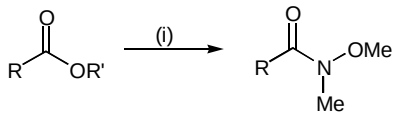
Scheme 1

Preparation of Weinreb's Amide (WA)

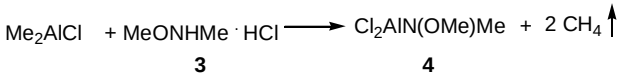
These amides have been prepared from acids and its derivatives. The amine, methoxy methyl amine [MeO(Me)NH] is commercially available in the form of its hydrochloride salt MeO(Me)NH · HCl (**3**). The hydrochloride salt **3** can be conveniently prepared [3] on a large scale starting from hydroxylamine hydrochloride. Among the derivatives of acids it is the acid halides which have been conveniently converted to Weinreb amides with ease [4]. Although the reactivity of the acid chlorides is high, it is not always possible to convert acids into acid chlorides particularly when the acid is multifunctional and contains sensitive functionalities and therefore other derivatives gain importance.

The esters and lactones have been invariably converted [5a–g] to Weinreb amides (Scheme 2) by using a combination of trimethyl aluminium and **3**, based on a procedure originally developed by Weinreb himself [5h–i]. Although this procedure using trimethyl aluminium in conjunction with the amine hydrochloride works excellently well, Shimizu *et al*. observed unsatisfactory results in case of sterically crowded lactones. This led to the development of an alternative combination [5j] of Me_2AlCl and **3** for the same purpose. Substantial improvement in the yields and in reaction periods was observed with this reagent. The real species formed *in situ* by combination of the reagent is Cl_2Al–NMe(OMe) (**4**), with concomitant evolution of two equivalents of methane. However, one should bear in mind that both the procedures with Me_3Al and Me_2AlCl necessitate the use of 2–5 equivalents of air sensitive aluminium reagent strictly under an inert atmosphere.





(i) Me_3Al, MeONHMe · HCl

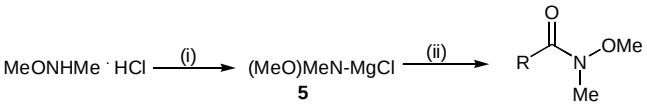


3 **4**

Scheme 2

  1436-9966/99/3410X-340 $ 17.50 + .50/0

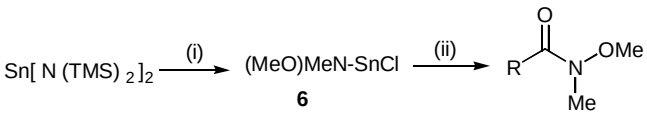
Interestingly, when trimethyl aluminium based conversion of esters to amides failed, again probably due to the carbonyl carbon of the esters being sterically crowded, William *et al*. observed [6] that the magnesium amide [Me(MeO)N–MgCl], (**5**) obtained by the reaction between **3** and non nucleophilic organo magnesium reagent such as *i*-propylmagnesium chloride has the necessary Lewis acidity and nucleophilicity to attack the carbonyl carbon of the ester (Scheme 3). In fact this alternative provided the *N*-methoxy-*N*-methyl amides in excellent yields. This method of converting esters to amides is gaining wide attention [7–9].



(i) *i*-PrMgCl, THF, 0 °C (ii) Methyl or Ethyl esters, 85–90%

Scheme 3

Lastly Roskamp *et al*. [10] observed that a combination of $Sn[N(TMS)_2]_2$ and **3** produces a reactive species [(MeO)MeN–Sn–Cl], (**6**) which also converts esters to amides (Scheme 4).



(i) MeO(Me)NH · HCl (ii) RCOOR' in THF; R'= Me, Et, Bn

Scheme 4

Although, there is no use of amides as starting substrates for the preparation of WA, Evans *et al*. [11–14], Martin *et al*. [15] and Schreiber *et al*. [16] have converted the oxazolidine based imides **7** to the corresponding WA by using a combination of Me_3Al and **3** in CH_2Cl_2 or THF at –20 °C to 0 °C (Scheme 5).

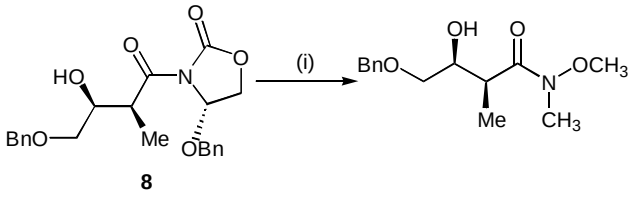
7

R^1 = Bn, R^2 = H
R^1 = R^2 = H, R^3 = Me, R^4 = H

(i) $AlMe_3$, MeONH(Me) · HCl in CH_2Cl_2 or THF

Scheme 5

Recently, Rinehart *et al*. [17] in their first report for the synthesis of unusual amino acid analogues, using Evan's aldol condensation, also brought about the conversion of imide **8** to WA using the same combination (Scheme 6).



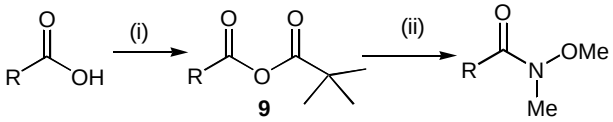
8

(i) Me_3Al,NH (OMe)Me · HCl, 89%

Scheme 6

It is the direct conversion of an acid to an amide which becomes very attractive as it obviates the need to first convert the acid to the derivative. This direct conversion relies on *in situ* activation of acids to attack of *N*-methoxy-*N*-methyl amine. To this end, several acid activating agents [18, 19] have been successful. These include DCC [20], DEPC [21], HOBT/DCC [22], HOBT/EDCI [17], BOP·PF_6 [23], CDI [24–26], alkyl chloroformate [27], CBr_4/TPP [28], 2-halo-1-alkylpyridinium salts [29] and py·BOP [30] EDCI [31], PPA [32]. A combination of PPh_3/NBS has also been found to be useful for effecting a direct conversion of acids to WA [33].

The advantage of the mixed anhydride wherein the carbonyl groups differ substantially due to steric factor has not been put to use for the formation of WA. Exploring this, we [34] recently reported a convenient high yielding procedure for the synthesis of WA both from chiral and achiral carboxylic acids using extremely cheap and readily available pivaloyl chloride as activating agent (Scheme 7). It is clear that at –5 °C to 0 °C, the attack of the amine on the pivaloyl carbonyl carbon in the mixed anhydride **9** is precluded due to steric factors and hence good yields of the desired WA are obtained.



9

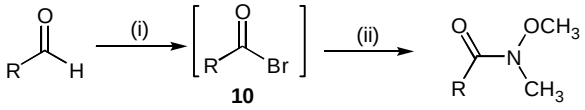
R = alkyl, aryl, heteroaryl

(i) 1.0 equi. of PivCl; 1.1 equi. of Et_3N in CH_2Cl_2 at 0 °C;
(ii) 1.2 equi. MeONHMe · HCl; 2.6 equi. of Et_3N

Scheme 7

Until our findings [33] there existed no report wherein aldehydes were directly converted to WA. Aldehydes

under oxidative conditions using *N*-bromosuccinimide and catalytic AIBN produced *in situ* the acylbromides **10** which on reaction with **3** in presence of triethylamine afforded the WA (Scheme 8).



R= alkyl, aryl, heteroaryl

(i) 1.0 equi. NBS, cat. AIBN, CCl_4, heat

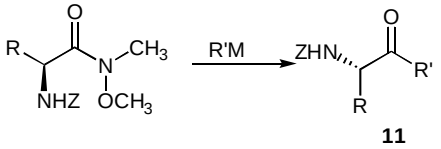
(ii) (MeO)NHMe · HCl, TEA, 70–75% Yield

Scheme 8

Applications of Weinreb's Amide (WA)

I. Synthesis of Ketones

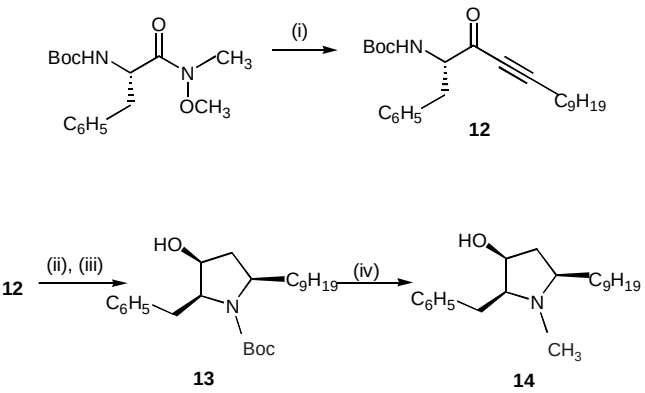
The synthesis of ketones has been the most important application of WA [35]. The synthetic operations involve reaction with various organometallics, R'M (R = alkyl, alkenyl, alkynyl, aryl, heteroaryl and M = MgX or Li) leading to formation of the new C–C bond and functional group conversion from amide to ketones exclusively. Due to the great importance of enantiomerically pure *N*-protected α-amino ketones **11** in preparative organic chemistry of biologically active substances, and also as interesting intermediates in natural product synthesis, WA have received attention for the synthesis of this class of compounds [36, 37] (Scheme 9). In fact, due to the ready availability of enantiomerically pure α-amino acids, the corresponding WA are becoming commercially available as valuable intermediates [38].



R = Me, *i*-Pr, Ph, $MeSCH_2$;
R'M = *n*-BuC≡C–Li, $(CH_3)_2CHCH_2CH_2MgBr$
Z = COOEt, SO_2Ph

Scheme 9

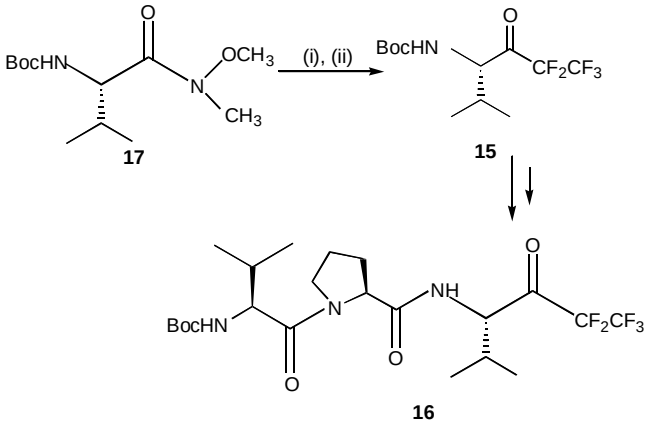
The strategy employed for the synthesis [20g] of (+) preussin **14**, an antifungal agent, invoked ynone **12** as a key intermediate wherein 5-*endo-dig* cyclization would afford pyrrolidinol **13**. The ynone **12** was conveniently obtained in 87% yield by reaction of decynyllithium in THF at –23 °C with WA of *t*-BOC-(S)-phenyl alanine (Scheme 10).



(i) LiC≡CC_9H_{19}, THF, –23 °C, 87% (ii) $Hg(OAc)_2$, NaCl
(iii) $NaBH_4$, 88% (iv) LAH

Scheme 10

The α amino pentafluoroethyl ketones **15** (Scheme 11) needed for the synthesis [39] of **16**, a potent inhibitor of human neutrophil elastase, was obtained by addition of pentafluoroethyl lithium to the WA **17**. This route appears to be the most versatile for synthesis of **16**.



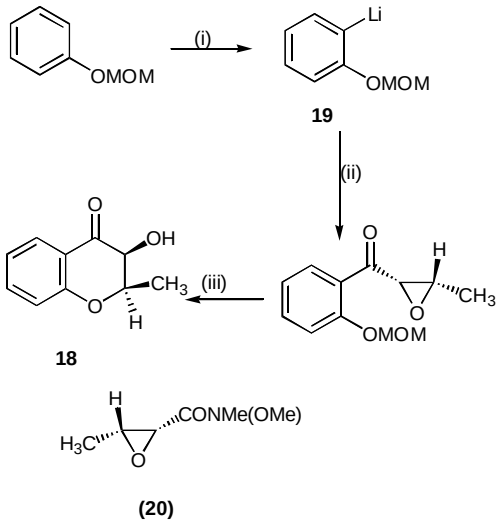
(i) CF_3CF_2Li, ether (ii) HCl, EtOAc

Scheme 11

Recently [40], novel access to hitherto unknown enantiopure 2-methyl chroma-4-ones **18** has been made by reaction of *ortho* metallated *O*-MOM-protected phenols **19** with WA **20** of enantiopure *cis*- or *trans*- glycidic acids(Scheme 12).

II. Synthesis of Aldehydes

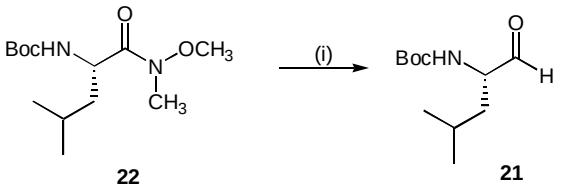
As mentioned earlier, due to ready availability of enantiomerically pure WA of α–amino acids, the access to optically pure α–amino aldehydes has become easy. In fact *N-tert*-butoxycarbonyl-*L*-leucinal **21** has been pre-



(i) *t*-BuLi (ii) **20** (iii) $HClO_4$, ethanol, H_2O

Scheme 12

pared on a large scale by satisfactory reduction of WA **22** with lithium aluminum hydride [41] (Scheme 13). As against the preparation of optically pure α–amino aldehydes, only a single report [42] exists in the literature for preparation of enantiopure *N*-protected β-amino aldehydes from WA.

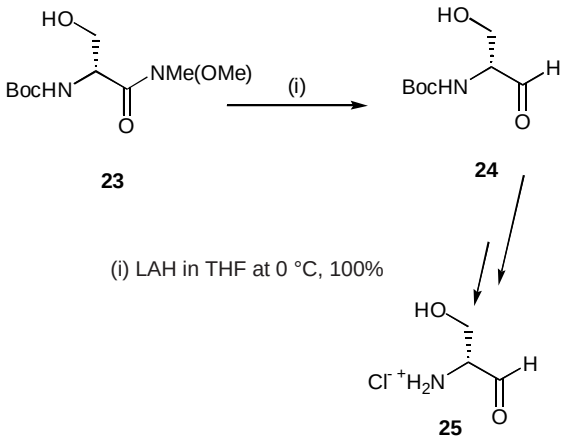


(i) $LiAlH_4$, ether, 87-88%

Scheme 13

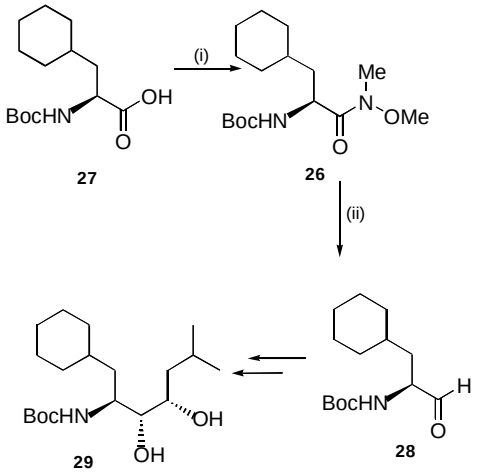
With a view to obtain multigram quantities of enantiomerically pure vinyl glycinyl hydrochloride **25** (Scheme 14) through Wittig olefination of Garner aldehyde **24**, Campbell [31a] *et al*. banked on quantitative reduction of the corresponding WA **23** to obtain **24**. This example illustrates the potential WA functionality holds in being stable precursor to sensitive aldehydes such as **24**.

Another elegant work by Schwindt [43] and his group from the laboratory of Parke-Davis, serves as an excellent example to illustrate the scale up to which these amides have been prepared and successfully reduced to



Scheme 14

the aldehyde stage (Scheme 15). WA **26** was prepared on 33 Kilograms scale from the acid **27** and reduced with Vitride [sodium bis (2-methoxyethoxy)aluminum hydride] in toluene at –15 °C to aldehyde **28**. It further paved the way for a convenient synthesis of **29** which is an important segment of CI-992, a compound Parke-Davis developed for the treatment of hypertension and congestive heart failure.

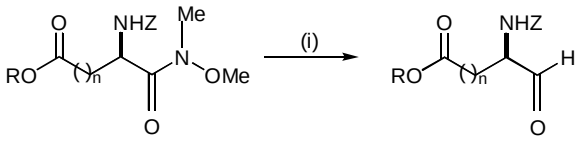


(i) ClCOOEt, MeNH(OMe) · HCl,Et_3N, 91% (ii) Vitride, 100%

Scheme 15

Martinez and coworkers [44] have shown that WA derivatives of amino and side chain protected aspartic and glutamic acids, **30** and **31**, respectively, can be reduced to the corresponding aldehyde by reduction with lithium tris (*tert*-butoxy)aluminium hydride [LiAl(O-*t*-Bu)$_3$H] and lithium tris-[(3-ethyl-3-pentyl)oxy]aluminium hydride [LTEPA] in THF at room temperature (Scheme 16) It is interesting to note that the benzyloxy carbonyl and *tert*-butoxycarbonyl protection of amino

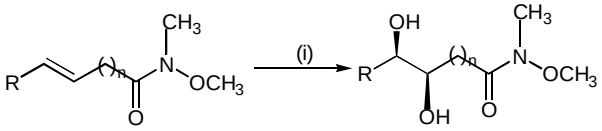
functional group as well as cyclohexyl and *tert*-butyl ester protection of the side chain carboxyl group of both the acids are stable under these reaction conditions.



30: n=1 aspartyl series
31: n=2 glutamyl series
R=*t*-butyl or cyclohexyl
Z=BnOCO- or *t*-BuO-CO-
(i) LiAl(O*t*-Bu)$_3$H or LTEPA /THF at room temp.

Scheme 16

Since unsaturated (α,β and β,γ) ketones and aldehydes are proven to be poor substrates for asymmetric dihydroxylation (AD), the excellent success [45] with the corresponding WA **32**, with modified AD-mix-β^{TM} (Scheme 17) becomes highly important as it would serve as a masked equivalent. AD-mix-β^{TM} is a solid mixture [46] of potassium osmate, $(DHQD)_2$-PHAL (an asymmetric ligand), potassium ferricyanide and potassium carbonate. The modified version involves five-fold increase in asymmetric ligand and potassium osmate content compared to the original formulation [46]. This new methodology was used to achieve a formal synthesis [47] of natural (+)-coriolic acid.

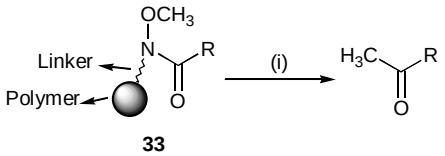


32

(i) Modified - AD - mix - β^{TM}
$CH_3SO_2NH_2$, *t*-BuOH-H_2O; 0 °C or RT;
yield - 81-97%

Scheme 17

Armstrong [22b] *et al*. have replaced the *N*-methyl group in WA by a linker that attaches this valuable functionality to a polymer and have succeeded in developing a route for aldehydes and ketones by performing reaction with Weinreb-type amides **33** on a solid support (Scheme 18).

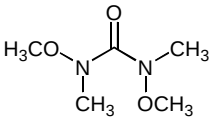
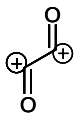
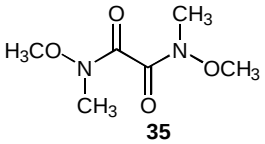
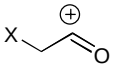
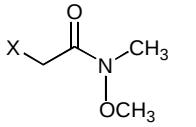
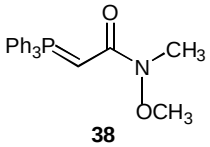
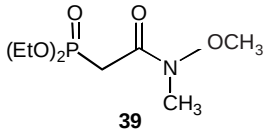
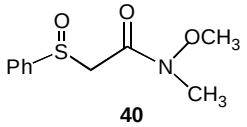
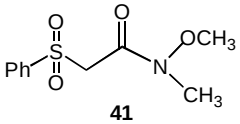


33

(i) CH_3MgBr, 77% yield

Scheme 18

Table 1 Various synthetic equivalents containing Weinreb amide functionality

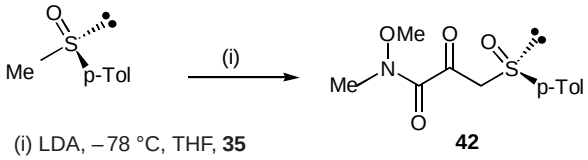
synthons	Synthetic equivalents
	 **34**
	 **35**
	 **36**: X = Cl **37**: X = NC
= CHCHO = CHCOR	 **38**
= CHCHO = CHCOR	 **39**
	 **40**
	 **41**

III. Valuable Reagents Containing Weinreb's Amide (WA) Functionality

Various synthetic equivalents based on Weinreb amide's functionality **34** to **41** has been listed in Table 1.

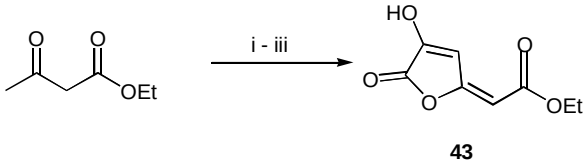
Hlasta [48] and Reich [49] have independently shown that *N,N'*-dimethoxy-*N,N'*-dimethyl urea (**34**) functions as a carbon dioxide equivalent providing unsymmetrical ketones on sequential treatment with two different nucleophiles. Similarly Sibi's [50] *N,N'*-dimethoxy-*N,N'*-dimethyl ethandiamide (**35**) has been useful for the synthesis of symmetrical α-diketones and α-oxo-WA.

Very recently [51], the same amide **35** was used to synthesise **42** for studying the sulfoxide directed stereoselective reduction of 1,2-diketo-derivatives [51a] (Scheme 19) and for regio- and stereoselective synthesis [51b] of γ-alkylidene butenolides **43** by reaction of the dilithio derivative of the 1,3-dicarbonyl compound and amide **35** (Scheme 20).



(i) LDA, – 78 °C, THF, **35** **42**

Scheme 19

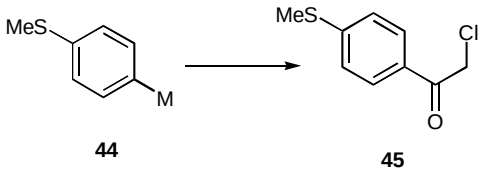


43

(i) 2.7 equi. LDA, (ii) 1.0 equi **35,** (iii) aq . HCl

Scheme 20

Tillyer observed [52] that chloroacetamide (**36**) (Table 1), on reaction with organometallics **44**, paved the way for an efficient synthesis of 4-(methylthio)-2-chloroacetophenone (**45**). The access to this chloroketone by all ways was found to be problematic (Scheme 21).



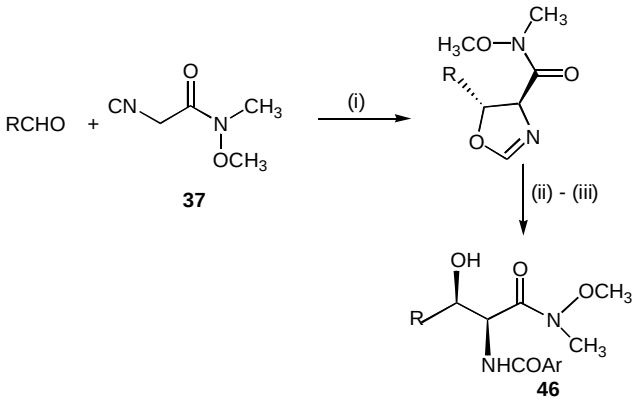
44 **45**

M = MgBr or Li

Scheme 21

α-Isocyano-WA **37**, which is synthetically equivalent to isocyano acetaldehyde and isocyanomethyl alkyl ketones is easily made on a multigram scale and was found to undergo clean asymmetric aldol reaction with a variety of aldehydes in presence of a gold(I) catalyst, thus providing an efficient synthesis of *N,O* protected β-hydroxy-α-amino aldehydes and ketones, **46** [53] (Scheme 22).

Evans [54] combined the usefulness of WA and phosphorane chemistry and thereby developed reagent **38**.

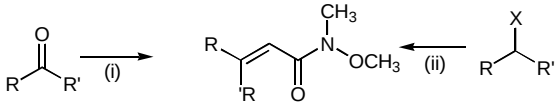


37 **46**

(i) Cat: [Au (C-HexNC)$_2$]BF_4; CH_2Cl_2 (ii) conc.HCl;MeOH
(iii) ArCOCl

Scheme 22

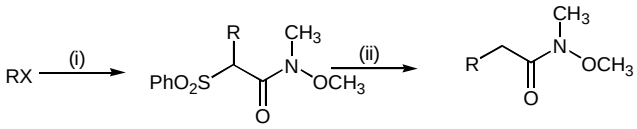
Siedel [55] and Nullizard [56] independently reported the Horner-Wadsworth-Emmons variant **39** and its utility. The building blocks **38** and **39** are useful agents for homologating aldehydes [57] and ketones [58] to α,β-unsaturated WA. Boumendjel very recently developed **40** to arrive at α,β-unsaturated WA from alkyl halides, instead of aldehydes and ketones [59] (Scheme 23).



(i) for **38**, toluene,reflux; for **39**, DBU / CH_3CN / R.T. (ii) **40**, NaH, DME

Scheme 23

Finally, we have developed [60] **41** for two carbon homologation of alkyl halides. This reagent combines the usefulness of the WA functionality with sulphone chemistry. It undergoes clean alkylation with various alkyl halides (Scheme 24) under mild conditions of K_2CO_3 in DMF. Subsequent desulphonylation leads to a two carbon homologated product containing stable and valuable functionality for further synthetic endeavours.

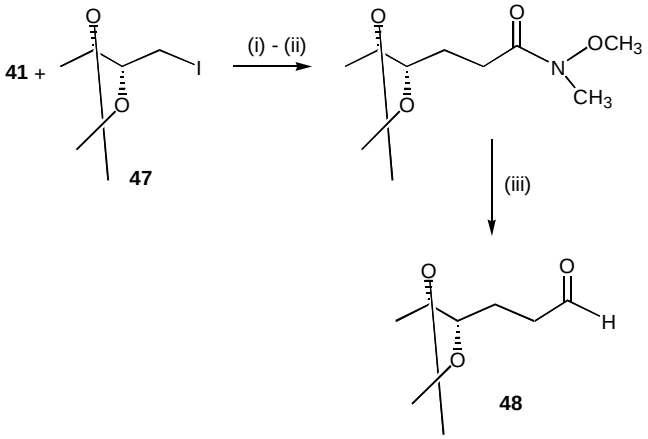


X = I, Br, Cl
R = alkyl, sugar residues

(i) **41**, K_2CO_3, dry DMF, (ii) Na (Hg), Na_2HPO_4, MeOH, 0 °C

Scheme 24

Successful chain extension of five and six carbon sugar halides containing sensitive functionalities has been achieved. In a separate work using **41** we have recently chain – extended *L*-threo configurated iodide (**47**), thereby accomplishing an efficient synthesis of 4,5-*O*-isopropylidene – protected *L*-rhodinose **48**, an important trideoxy sugar [61] (Scheme 25).



(i) K_2CO_3, dry DMF, 60 °C, 73% (ii) Na (Hg), Na_2HPO_4, MeOH, 0 °C, 67% (iii) LAH, THF, –78 °C, 76%

Scheme 25

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[19] List of abbreviations: DEPC: Diethyl phosphorocyanimidate, EDCI: *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, PPA: Propylphosphonic anhydride, DCC: Dicyclohexylcarbodiimide, HOBt: 1-Hydroxybenzotriazole, BOP:PF_6: Benzotriazol-1-yloxytris (dimethylamino)-phosphonium hexafluorophosphate, CDI: *N*,*N'*-Carbonyldiimidazole, TPP: Triphenylphosphine.
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Address for correspondence:
Dr. Indrapal Singh Aidhen
Department of Chemistry
Indian Institute of Technology
Chennai (Madras) – 600 036
INDIA
Fax : Internat. code 0091–044–2350509
e-Mail: isingh@acer.iitm.ernet.in