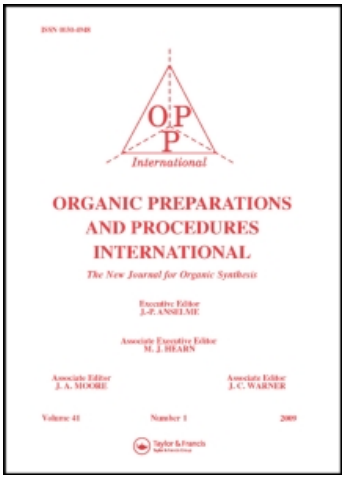

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CHEMISTRY OF N-METHOXY-N-METHYLAMIDES. APPLICATIONS IN SYNTHESIS. A REVIEW

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CHEMISTRY OF N-METHOXY-N-METHYLAMIDES. APPLICATIONS IN SYNTHESIS. A REVIEW

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Fargo, ND 58105, USA

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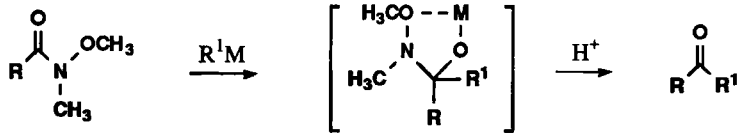
INTRODUCTION

Since the initial report of Nahm and Weinreb[1] on the use of N-methoxy-N-methylamides **1** as carbonyl equivalents, this functional group has enjoyed tremendous popularity (Scheme 1). The main reasons for the utility of this synthon are the ease of preparation, few side-reactions during nucleophilic addition and selective reduction to form aldehydes. These advantages can be ascribed to the stability of the tetrahedral intermediate **2** formed by addition of nucleophiles to N-methoxy-N-methylamides due to chelation. This review is limited to the discussion of the utility of N-methoxy-N-methylamides,[2] and chemistry of other related carbonyl synthons will not be discussed.

Scheme 1



1 **2**

The review is divided into three main sections. The first section describes the various methods for the preparation of N-methoxy-N-methylamides from carboxylic acids and their derivatives. The second section details the preparation of a variety of carbonyl compounds (ketones) by nucleophile addition. The third section describes the reduction of N-methoxy-N-methylamides to aldehydes and alcohols by hydride reagents.

I. SYNTHESIS OF N-METHOXY-N-METHYLAMIDES

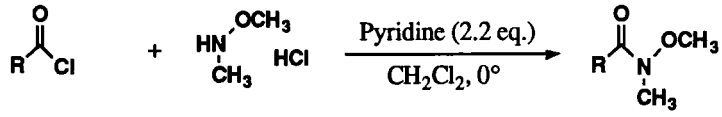
There are several methods available for the synthesis of N-methoxy-N-methylamides. These are illustrated using an example from each category in this section.

1. Synthesis from Acid Chlorides

It is relatively straightforward to convert an acid chloride to an N-methoxy-N-methylamide. Treatment of an acid chloride (in methylene chloride or chloroform) and N,O-dimethylhydroxylamine hydrochloride at 0° with 2.2 equivalents of pyridine affords the corresponding amides in excellent yields (Eq. 1).

The product isolation is carried out by aqueous workup. The product amides are stable and can be purified readily by chromatography, crystallization, and/or distillation. N,O-dimethylhydroxyl-

amine hydrochloride is commercially available (moderately expensive). A convenient procedure for



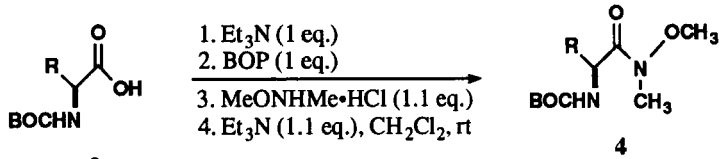
(1)

R = Alkyl, Aryl, Heterocyclic, etc. (90-100%)

the preparation of the starting N,O-dimethylhydroxylamine has also been reported.[3]

2. Synthesis from Carboxylic Acids

The N-methoxy-N-methylamides can also be prepared from the corresponding carboxylic acid by a variety of coupling procedures. The normal peptide coupling reagents work quite well in these syntheses. Typical coupling reagents that have been applied for the preparation of amides are BOP (benzotriazol-1-yloxytris[dimethylamino]-phosphonium hexafluorophosphate),[4] DCC (dicyclohexyl-carbodiimide),[5] and others.[6] These procedures are especially useful for the preparation of amides **4** from α-amino acids **3** without any racemization of the chiral center (Eq. 2).

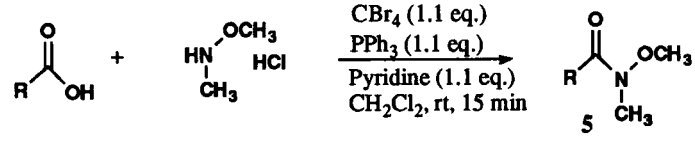


3 **4**

(2)

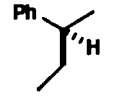
R	Yield, **4** (%)	R	Yield, **4** (%)
CH_3	85	$(CH_3)_2CH$	80
$CH_3(CH_3)CHCH_2$	94	$C_6H_5CH_2$	95
$CH_3CH_2(CH_3)CH$	70	$C_6H_5CH_2CO(CH_3)CH$	95

Recently, Einhorn *et al.* have developed a very mild and efficient method for the synthesis of N-methoxy-N-methylamides **5** from the corresponding carboxylic acids using carbon tetrabromide and triphenylphosphine (Eq. 3).[7]

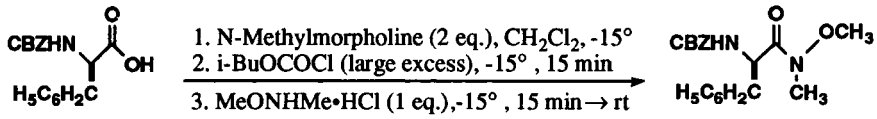


5

(3)

R	Yield, **5** (%)	R	Yield, **5** (%)
HC≡C–	52	$BrH_2C-(CH_2)_5-$	99
	75		76
	71		80

Angelastro and co-workers[8a,b] have used an *in situ* mixed anhydride method for the synthesis of N-methoxy-N-methylamides **6** from racemization prone N-protected-α-amino acids (Eq. 4). For



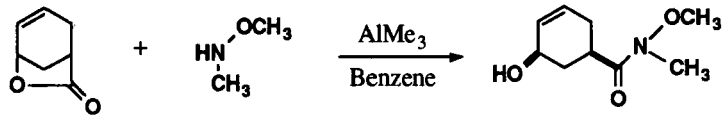
(4)

6 (91%)

example, N-CBZ-phenylalanine was treated with isobutyl chloroformate followed by N,O-dimethylhydroxylamine and N-methylmorpholine to furnish the corresponding amide in good yield.

3. Synthesis from Lactones and Amides

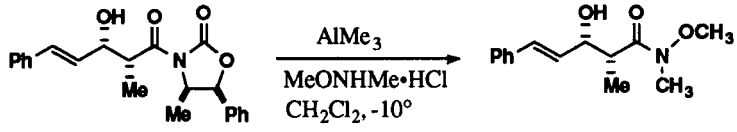
The reaction between the aluminum amide derived from N,O-dimethylhydroxylamine and lactones also provides a ready route to the N-methoxy-N-methylamides. Kocienski and co-workers have used this method for the preparation of cyclohexenecarboxamide **7** in good yield (Eq. 5).[9]



(5)

7 (91%)

Evans[10] has made use of the transamination procedure developed by Weinreb[11] in the preparation of many intermediates required in the construction of complex natural products. An example of the preparation of one such intermediate **8** is shown in Eq. 6. The aluminum amide solution is



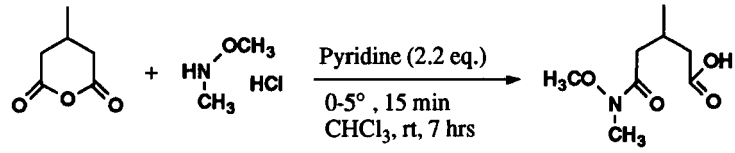
(6)

8 (100%)

prepared by careful addition of trimethylaluminum in toluene to a suspension of N,O-dimethylhydroxylamine hydrochloride in methylene chloride at 0°.

4. Synthesis from Anhydrides

The N-methoxy-N-methylamides can also be obtained from the corresponding anhydrides and N,O-dimethylhydroxylamine by nucleophilic displacement. Eq. 7 illustrates an application of this method in the synthesis of the half amide acid **9** derived from glutaric acid.[12]

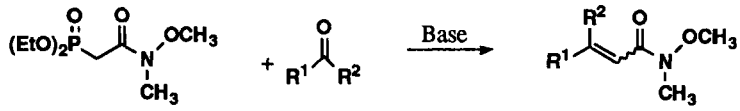


(7)

9 (96%)

5. Synthesis of α,β-Unsaturated Amides

α,β-Unsaturated N-methoxy-N-methylamide can be obtained from either the corresponding carboxylic acid or a stabilized Wittig[13] or Wittig-Horner reagent.[14] Reactions with these easily synthesized reagents work well providing the amides in good to excellent yields. Three groups[14a,b,c] have reported the preparation and use of diethylphosphonate reagent **10** in the synthesis of α,β-unsaturated N-methoxy-N-methylamides. The chemistry of the dimethylphosphonate analog of **10** has also been reported.[14d] The reactions of aldehydes with phosphonate **10** proceed in good yields providing amides **11** with very high *E* selectivity (Eq. 8 and Table 1). Sodium hydride, alkyllithiums, DIPEA/LiCl, and DBU/LiCl have been used as the deprotonating agents in these reactions.



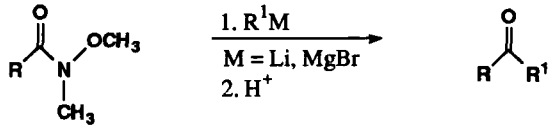
10 **11** (8)

TABLE 1. Synthesis of α,β-Unsaturated Amides from Phosphonates **10**

Carbonyl Compound	Base	*E*/*Z*	Yield, **11** (%)	Reference
Heptanal	n-BuLi	95/5	76	14a
Heptanal	NaH	95/5	94	14b
Benzaldehyde	n-BuLi	95/5	74	14a
Benzaldehyde	NaH	100/0	91	14b
Citral	NaH	100/0	89	14b
Citral	DIPEA/LiCl	100/0	40	14b
Citral	DBU/LiCl	100/0	91	14b
β-Cyclocitral	n-BuLi	100/0	71	14c
Acetophenone	NaH	81/19	76	14b
Cyclohexanone	n-BuLi	-	82	14a
Cyclohexanone	DBU/LiCl	-	72	14b

II. NUCLEOPHILIC ADDITIONS TO N-METHOXY-N-METHYLAMIDES. SYNTHESIS OF CARBONYL COMPOUNDS

The reaction between N-methoxy-N-methylamides and nucleophiles provide a general route to the synthesis of ketones. These reactions proceed in good to excellent yields under fairly mild conditions (Eq. 9).[15]



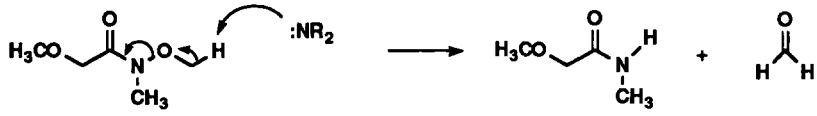
(9)

The reactions work equally well with alkyllithiums as well as Grignard reagents. The reactions are generally carried out at -78° or 0°, and solvents such as THF, ether, or DME have been used for these reactions. A large number of nucleophiles with variation in structure have been used to prepare

ketones, and these are discussed based on the functional group type (vide infra). These reactions are highly selective and the formation of alcohols by over addition of the nucleophile is rarely observed.

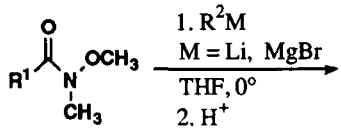
In certain cases during nucleophilic addition with hindered and/or highly basic reagents, the N-methoxy-N-methylamides show unusual reactivity. Graham and Scholz[16] have shown that carbanions derived from thiophene-2-sulfonamides react with N-methoxy-N-methylamides to provide N-methylamides and formaldehyde (Scheme 2). Similar observations have also been made by two other groups.[17] The mechanism of this reaction has been postulated to involve an E2 pathway.

Scheme 2



1. Synthesis of Ketones

The main application of N-methoxy-N-methylamides has been in the preparation of ketones. Weinreb[1] in his seminal studies showed that a variety of N-methoxy-N-methylamides undergo nucleophilic addition to provide ketones in good yields (Eq. 10). The typical workup procedure involves

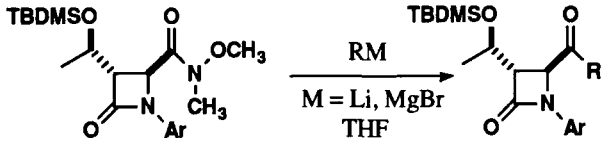


R^1	R^2	Yield (%)
Phenyl	Methyl	96
Phenyl	*n*-Butyl	91
Phenyl	Phenyl	95
Cyclohexyl	Phenyl	100
Cyclohexyl	*n*-Butyl	97
Cyclohexyl	PhC≡C	92

(10)

quenching of the reaction with dilute hydrochloric acid to decompose the chelated intermediate followed by aqueous/organic solvent extraction.

In a useful application of the N-methoxy-N-methylamides, Prasad and Liebeskind[18] have applied the methodology to the preparation of a variety of functionalized β-lactams **12** in moderate to good yields (Eq. 11).



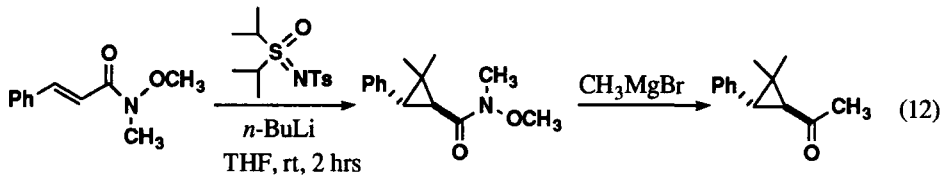
Ar = 4-methoxyphenyl

12

R	Yield, **12** (%)
Methyl	99
PhC≡C	93
TMSC≡C	75
$PhCH_2$	47
Allyl	99
Vinyl	45

(11)

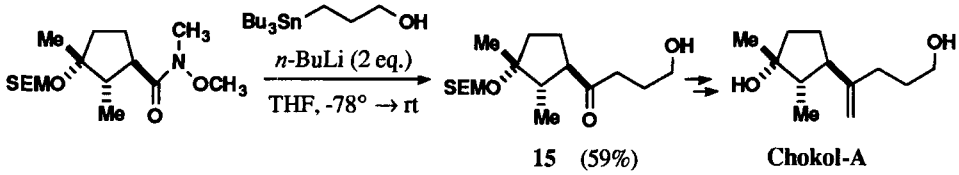
Rodriques[19] has prepared cyclopropyl ketone **14** from the corresponding N-methoxy-N-methylamide **13**. The cyclopropanamide itself was prepared in good yields using a sulfur ylide and the corresponding α,β-unsaturated amide (Eq. 12). The cyclopropanation with the corresponding unsaturated ketone proceeded in poor yields. The higher yield with the amide was attributed to the directing ability of the methoxy group during cyclopropanation.



(12)

Oppolzer and Cunningham, in their synthesis of racemic Chokol-A, used a dilithio alkoxide to prepare an advanced intermediate **15** in moderate yield as shown in Scheme 3.[6a]

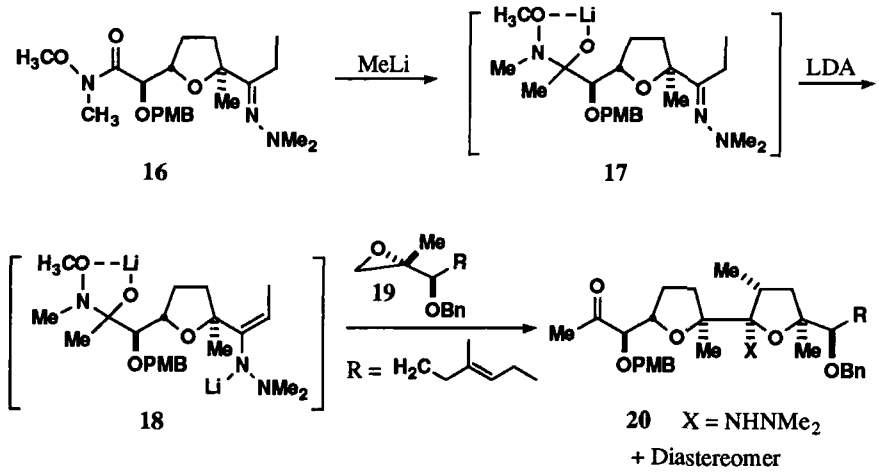
Scheme 3



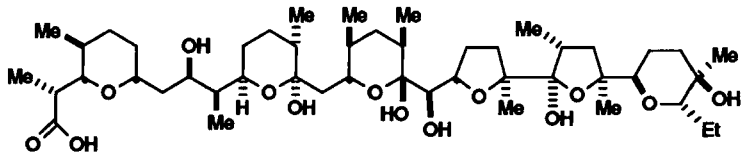
2. Utility of Tetrahedral Intermediate in Remote Functionalization

Evans[20] has elegantly made use of the stability of the tetrahedral intermediate formed by the addition of a nucleophile to N-methoxy-N-methylamide, thus allowing for further functionalization at a remote site within the same molecule (Scheme 4). Treatment of the amide/Schiff base **16** with

Scheme 4



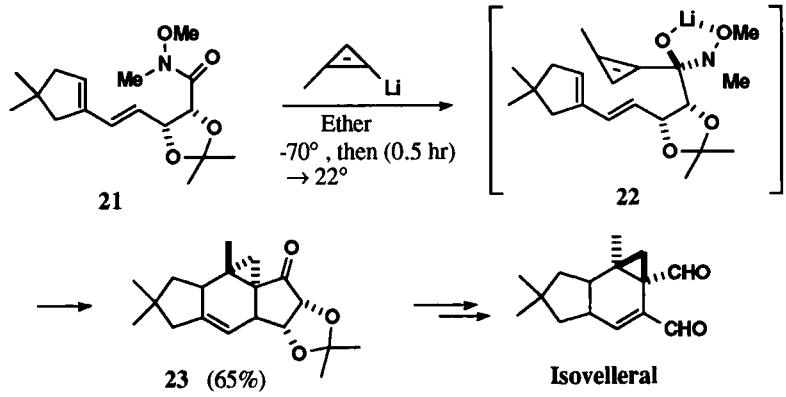
the tetrahedral intermediate **17**, which was metallated *in situ* using LDA furnishing the intermediate **18**. This was then quenched with epoxide **19** to produce **20**, an advanced intermediate in the synthesis of polyether antibiotic X-206.



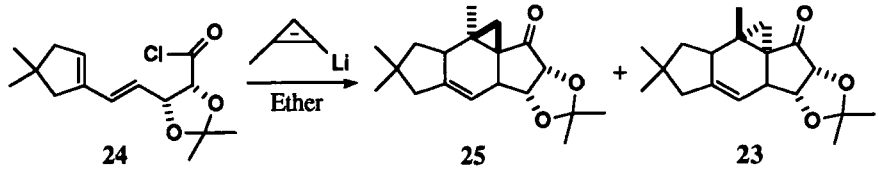
X-206

Bergman *et al.* have utilized the tetrahedral intermediate in an innovative fashion in the total synthesis of the sesquiterpene natural product (+)-isovelleral.[21] Reaction of the N-methoxy-N-methylamide **21** with methylcyclopropenyl lithium produced the tetrahedral intermediate **22** which underwent spontaneous intramolecular Diels-Alder cyclization to furnish the pentacyclic ketone **23** in 65% yield (Scheme 5).

Scheme 5



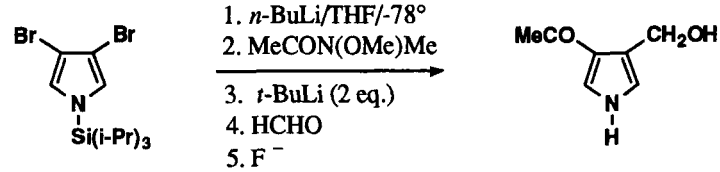
On the other hand, formation of the cyclopropenyl ketone by the treatment of the corresponding acid chloride **24** with methylcyclopropenyl lithium, gave a 10:1 mixture of stereoisomers **25** and **23** in a combined yield of 9% after intramolecular Diels-Alder cyclization (Eq.13). The facile cyclization in the case of the amide has been attributed to conformational restraints exerted by the ketal ring in the chelated intermediate.



(13)

9% Combined Yield, **25**:**23** = 10:1

Bray *et al.* have taken advantage of the stability of the tetrahedral intermediate in the synthesis of verrucarin E, a weak antibiotic.[22] Thus, treatment of the N-protected 3,4-dibromopyrrole with n-BuLi followed by quenching with N-methoxy-N-methylacetamide provides the chelated intermediate (Eq. 14). This is further metallated without isolation and quenched with formaldehyde. Final silyl



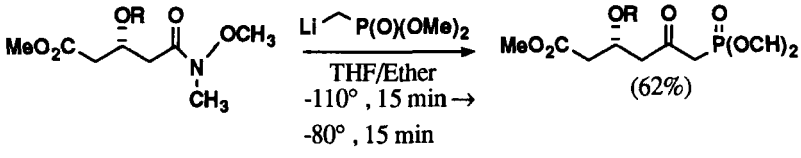
(14)

26 (44%)

deprotection provided verrucarin E **26** in 44% overall yield. The above examples illustrate that the stability of the tetrahedral intermediates can be cleverly used in synthetic sequences.

3. Chemoselectivity in Nucleophilic Addition

Thiesen and Heathcock[23] have exploited the chemistry of N-methoxy-N-methylamides in the preparation of useful Wadsworth-Emmons reagents required for the synthesis of mevinic acid analogs (Eq. 15). The reaction illustrates the chemoselectivity in nucleophilic addition to this multifunctional starting material. Heathcock observed that the attack of the anion took place exclusively at the amide

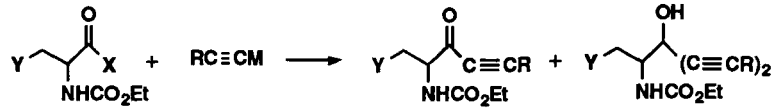


(15)

along with minor amounts of β-alkoxy elimination products. No products from anion attack at the ester site were observed. A similar chemoselectivity has also been observed by Guingant.[24]

4. Comparative Study

Rapoport and co-workers[25] have evaluated a variety of carboxylic acid derivatives in the preparation of ynones **27** (Eq. 16). They showed that N-methoxy-N-methylamides are very inert to

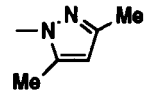
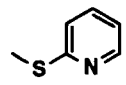


(16)

Y = H, Ph, CH_2SMe R = Alkyl **27** **28**

excess nucleophilic attack as compared to acid chlorides, lithium carboxylates, 2-pyridylthioate ester, and N-acylpyrazoles and result in no tertiary alcohol products (Table 2, compare entry 6 with entries 1-5). The reactivity of the N-methoxy-N-methylamides was found to be comparable to isoxazolidides (entries 6 and 7).

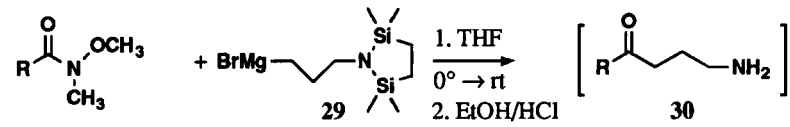
TABLE 2. Synthesis of Ynones. A Comparitive Study

Entry	X	M, mol%	27:28	Yield, 27 (%)
1	OH	Li, 350		No Reaction
2	Cl	Li, 110	1:2	<5
3	Cl	MgBr, 230	1:10	<1
4		Li, 100	1:10	<1
5		MgBr, 200	1:20	<1
6	$-N(CH_3)OCH_3$	Li, 250	>100:1	84
7		Li, 250	>100:1	88

5. Synthesis of Pyrrolidines

In a novel route to 2-substituted pyrrolidines, Basha and DeBernardis[26] have utilized an amino protected Grignard reagent **29** as a nucleophile and prepared the δ-amino ketone **30** (Scheme 6). Intermediates **30** were not isolated. These intermediates were converted to the pyrrolidines **31** by reduction of the imines using $NaBH_4$.

Scheme 6



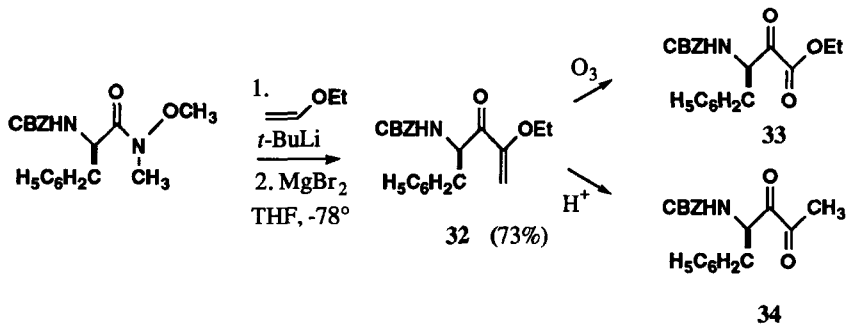
R	Yield, 31 (%)
Phenyl	70
Cyclohexyl	62
3-Pyridyl	60
2-Furyl	71
3-Butenyl	65
Benzyl	48

6. Synthesis of α-Amino Ketones

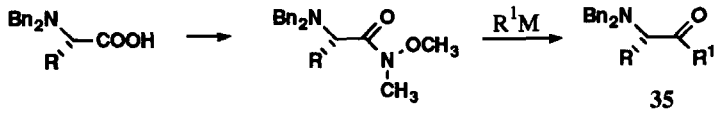
One of the key applications of N-methoxy-N-methylamides is in the synthesis of α-heteroatom substituted carbonyl compounds. An example of one such application is illustrated in the synthesis of an intermediate **32** used for the preparation of α-ketoester **33** and α-diketone **34** derivatives of

N-protected amino acids (Scheme 7).[8a] The nucleophilic addition proceeds without any epimerization of the chiral center.[27]

Scheme 7



In connection with the preparation of α-amino alcohols by non-chelation controlled reduction, Reetz and co-workers[28] have prepared a series of α-amino ketones starting from the corresponding N,N-dibenzylamino acids. The preparation of the amino ketones **35** proceeds in good to high yields without any racemization of the chiral center using a variety of organometallic reagents (Eq. 17 and Table 3).



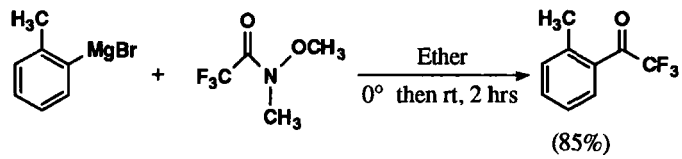
(17)

TABLE 3. Synthesis of α-Amino Ketones by Addition of Organometallic Reagents

R	R^1M	Yield, **35** (%)
$PhCH_2$	MeLi	94
$PhCH_2$	MeMgI	92
$PhCH_2$	EtLi	89
$PhCH_2$	n-BuLi	72
$PhCH_2$	PhLi	89
Me_2CHCH_2	MeLi	96
Me_2CHCH_2	n-BuLi	57
Me_2CHCH_2	PhLi	87
Me_2CHCH_2	2-Thienyl-Li	75
$BnOCH_2$	MeLi	78

7. Synthesis of Trifluoromethylketones

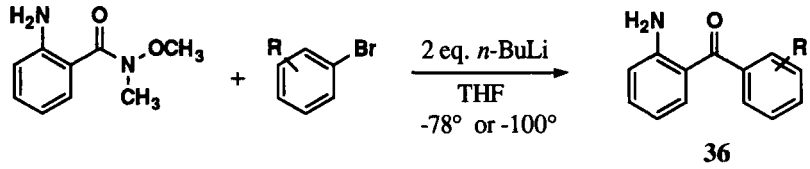
The N-methoxy-N-methylamide derived from trifluoroacetic acid serves as a very useful synthon for the preparation of trifluoromethyl ketones. An example of this in the preparation of substituted trifluoroacetophenone is shown in Eq. 18.[29]



(18)

8. Synthesis of 2-Aminobenzophenones. Halogen Metal Exchange and Nucleophilic Attack

Frye and co-workers[30] have cleverly utilized the differences in reaction rates between halogen-metal exchange and nucleophilic attack on N-methoxy-N-methylamides in the synthesis of benzodiazepine precursors. Treatment of a 1:1 mixture of 2-amino-N-methoxy-N-methylbenzamide and an aryl bromide with 2 equivalents of n-BuLi at low temperatures produced 2-aminobenzophenones **36** in moderate to good yields (Eq. 19 and Table 4). The amide starting material is readily obtained from



(19)

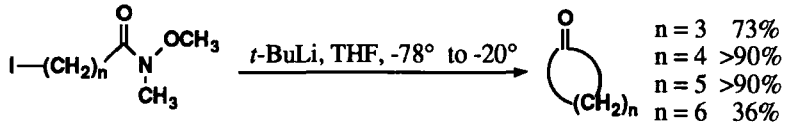
isatoic anhydride. t-BuLi was equally effective as n-BuLi in these reactions. These authors have drawn several interesting conclusions regarding the relative rates of deprotonations, halogen-metal exchange, and nucleophilic attack.

TABLE 4. Synthesis of 2-Aminobenzophenones

R	Temp. (°C)	Yield, **36** (%)
2-OCH_2Ph	-78	68
3-OCH_2Ph	-78	67
4-OCH_2Ph	-78	70
H	-78 or -100	70
2-CH_3	-78	55
3-Cl	-100	51
2-F	-100	35
4-CN	-100	40
4-CO_2t-Bu	-100	51

9. Synthesis of Cyclic Ketones

The N-methoxy-N-methylamides undergo intramolecular nucleophilic displacements to provide cyclic ketones.[31] The preparation of cycloalkanones **37** of varied ring size in moderate to good yields is shown in Eq. 20. The reaction with n = 2, 7, and 10 did not lead to cyclic products.



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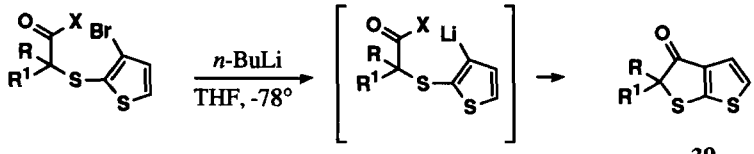
37

In connection with the preparation of potent inhibitors of human carbonic anhydrase II, Selnick and co-workers[32] have carried out intramolecular Parham like cyclizations (Scheme 8). The best yields in these reactions were obtained using the N-methoxy-N-methylamides **38a**, while the corresponding carboxylic acids **38b** or esters **38c** gave only modest yields of **39**. These experiments also show that halogen-metal exchange is faster than nucleophilic attack at the amide.

Scheme 8

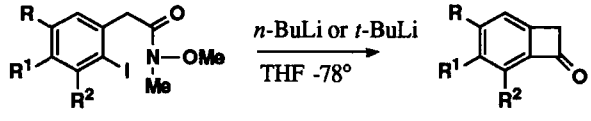


38a X = $N(CH_3)OMe$
38b X = OH
38c X = OR

39

	R	R^1	Yield, **39** (%)
Starting Material **38a**	H	Methyl	46
	Methyl	Methyl	51
	H	*n*-Propyl	75
	Methyl	*n*-Propyl	95

Aidhen and Ahuja have taken advantage of the fast halogen-metal exchange in the preparation of benzocyclobutanones (Eq. 21).[33] Treatment of the 2-iodo-N-methoxy-N-methylphenylacetamides with either n-BuLi or t-BuLi furnished the benzocyclobutanones **40** in moderate yields.



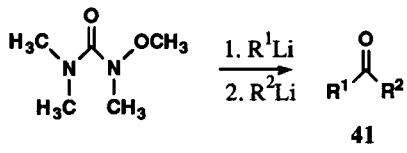
(21)

40

R	R^1	R^2	Yield, **40** (%)
H	H	H	62
-OCH_2O-		H	64
OMe	OMe	H	67
OMe	OMe	OMe	64

10. Synthesis of Symmetrical and Unsymmetrical Ketones. Carbon Dioxide Equivalent

Hlasta and Court[34] have devised an elegant one pot method to prepare unsymmetrical ketones using a carbon dioxide equivalent (Eq. 22). A similar sequence has also been reported by Whipple and



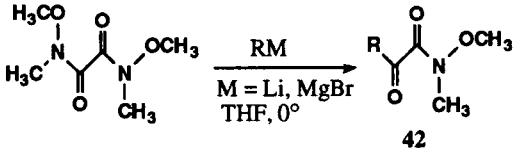
R^1	R^2	Yield, **41** (%)
Phenyl	*n*-Butyl	62
Cyclohexyl	Phenyl	41
Phenyl	2-Pyridyl	60
N-Me-2-Indolyl	Methyl	79

(22)

Reich.[35] The method involves the sequential treatment of N-methoxyurea derivative with two different lithium reagents at -78°. The reaction proceeds by *in situ* formation of N-methoxy-N-methylamides following initial nucleophilic addition and loss of the anion of dimethylamine. The addition of the second nucleophile then proceeds in the usual manner producing either the unsymmetrical or symmetrical ketone **41**, depending on the nature of the reagent.

11. Synthesis of α-Ketoamides

Sibi and co-workers[36] have explored the utility of a 1,2-dicarbonyl synthon derived from oxalic acid in the preparation of α-ketoamides and 1,2-diketones. The N,N'-dimethoxy-N,N'-dimethylethanediamide readily prepared from oxalyl chloride, reacts with either organolithiums or Grignard reagents to provide α-oxo-N-methoxy-N-methylamides **42** in good to excellent yields (Eq. 23).

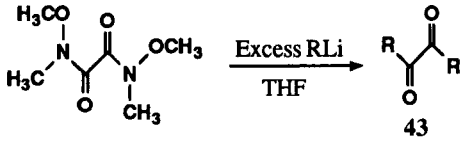


R	Yield, **42** (%)
Phenyl	95
p-Chlorophenyl	88
Benzyl	61
Cyclohexyl	70
n-Butyl	75

(23)

12. Synthesis of α-Diketones

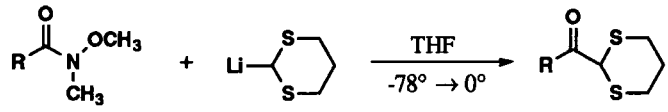
The ethanamide described in Eq. 23 also serves as a useful synthon for the preparation of 1,2-diketones **43**.[36] These reactions proceed well with aryllithiums. Aryl Grignards are less successful in this sequence (Eq. 24) resulting in the formation of the corresponding α-oxo-N-methylamides as the byproducts.



R	Yield, **43** (%)
Phenyl	76
p-Chlorophenyl	66
p-Tolyl	86
o-Methoxyphenyl	41
p-Methoxyphenyl	52

(24)

Guanti *et al.*,[37] in their approach to protected glyceraldehydes, have prepared a series of 2-acyl-1,3-dithianes in excellent yields by the reaction of lithiodithianes and N-methoxy-N-methylamides (Eq. 25).

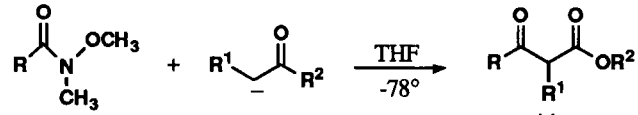


(25)

R = Me, Et, *n*-Hex., CF_3, CH_2OTHP, CH_2OAc, etc (80-95%)

13. Synthesis of β-Dicarbonyl Compounds

Turner and Jacks[38] have shown that enolates derived from ketones, esters, acetonitrile, and acetone dimethylhydrazone react with N-methoxy-N-methylbenzamide to produce carbonyl compounds **44** in moderate yields (Eq. 26). Following this precedent, Jones *et al.*[39] have prepared a



(26)

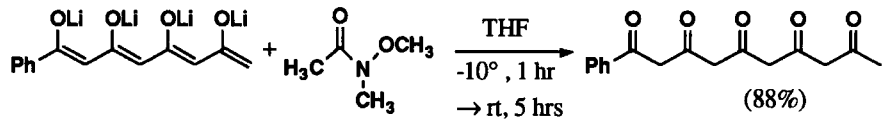
44

R	R^1	R^2	Yield, **44** (%)
Ph	H	*t*-Bu	83
Ph	Me	*t*-Bu	72
Ph	F	*t*-Bu	79
Benzyl	H	Et	63
n-Pentyl	H	*t*-Bu	80

variety of dimethylhydrazino enones in good yields. This is in contrast to the earlier work of Harris,[40] where he reported that ketone enolates failed to undergo reactions with N-methoxy-N-methylamides. Other inefficient condensations with ester enolates and N-methoxy-N-methylamides have also been reported.[41]

14. Synthesis of Oligo β-Diketones

Acetylations of the lithium salts of di-, tri-, and tetraanions of ketones with esters are generally problematic resulting in very low yields of the desired products. Oster and Harris[40] have presented a solution to this problem while investigating the utility of N-methoxy-N-methylamides in the preparation of oligo-β-diketones (Eq. 27). This work also reports several other examples of oligo-β-diketone



(27)

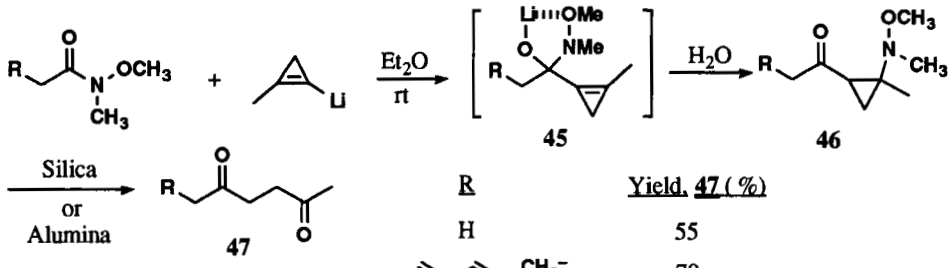
syntheses. A similar methodology has also been employed by Harris and co-workers[42] in an elegant biomimetic syntheses of polyketide natural products pretetramides.

15. Synthesis of 1,4-Dicarbonyl Compounds

Bergman *et al.* have devised an interesting route to the synthesis of 1,4-diketones (Scheme 9).[43] Treatment of a variety of N-methoxy-N-methylamides with 2-methylcyclopropenyl lithium in

ether at ambient temperatures furnishes the tetrahedral intermediate **45**. This intermediate eliminates N,O-dimethylhydroxylamine, which then adds in a Michael fashion to the resultant cyclopropenone to provide the cyclopropylketone **46**. The cyclopropyl ketones are then converted to the 1,4-diketones **47** by treatment with silica or alumina in good to excellent yields. The methodology has been successfully applied to the synthesis of *cis*-jasmone. An alternate pathway for the intermediate adduct leading to an intramolecular Diels-Alder product was discussed earlier.

Scheme 9

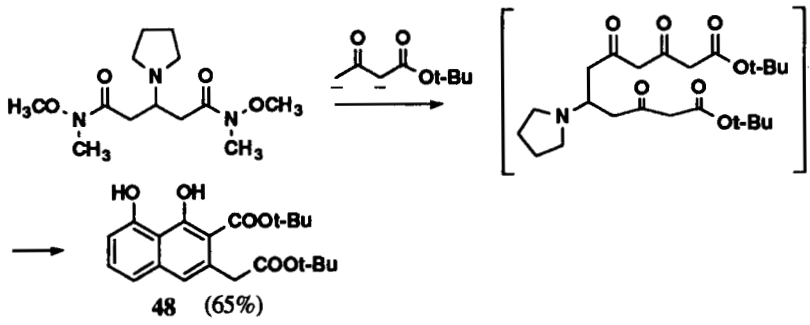


R	Yield, **47** (%)
H	55
CH_2^-	79
CH_2^-	86
CH_2^-	90
CH_2^-	85
CH_2^-	75

16. Synthesis of 1,5-Dicarbonyl Compounds

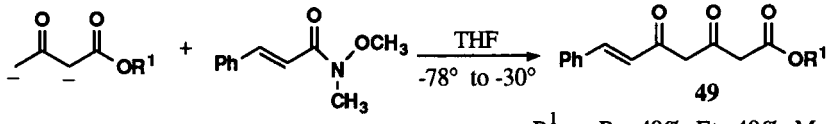
Harris and co-workers[42] in their biomimetic synthesis of pretetramide have successfully used a 1,5-dicarbonyl synthon to prepare a key intermediate. The diamide synthon was synthesized by the reaction of 6-chloro-2-pyrone with N,O-dimethylhydroxylamine followed by addition of pyrrolidineto the resultant unsaturated amide. This diamide undergoes condensation with the dilithium salt of tert-butyl acetoacetate to furnish the naphthalene diester **48** in 65% yield (Scheme 10). A similar reaction starting with the substituted diethyl glutarate gave very low yields of the naphthalene diester.

Scheme 10



17. Reactions of α,β-Unsaturated Amides

In an approach to the synthesis of β,δ-diketoesters, Hanamoto and Hiyama[44] have evaluated the chemistry of α,β-unsaturated amides as starting materials. The result from the reaction of the dianion of several acetoacetic esters with the N-methoxy-N-methylcinnamide is shown in Eq. 28. The reactions proceed cleanly providing the keto esters **49** in moderate yields. No trace of conjugate addition products was detected. On the other hand, reactions of the ester enolates with dimethylcinnamide, cinnamoyl chloride, or 1-cinnamoylimidazole gave a complex mixture of products. Trost and Schmidt[45] have also reported the preparation of ynones in high yields from N-methoxy-N-methylcinnamide. Preparation of α,β-unsaturated ketones from reactions of N-methoxy-N-methyl-3,3-dimethylacrylamide with nucleophiles has been reported.[46]



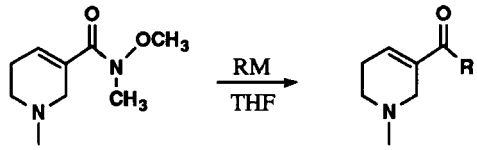
49

(28)

R^1 = *t*-Bu, 49%; Et, 49%; Me, 57%

In contrast to the above successful chemoselective reactions of α,β-unsaturated amides, Rapoport and co-workers[47] have reported that N-methoxy-N-methylamides derived from *trans*-cinnamic acid and β,β-dimethylacrylic acid furnished multiple products on reaction with 5-lithioindole. The presence of the α,β-unsaturated ketone in these experiments was detected by ^{1}H NMR, but none of the desired material could be isolated.

Ward and Merritt[48] have evaluated the effect of both temperature and nature of the metal on nucleophilic addition to tetrahydropyridinecarboxamide **50** (Eq. 29). Reactive Grignard reagents gave



50 **51**

(29)

better yields of the ketones (Table 5) while less reactive Grignard reagents gave poor yields (compare entries 1 and 9 with 2). On the other hand, the corresponding organolithiums gave higher yields as

TABLE 5. Addition of Organometallic Reagents to α,β-Unsaturated Amides

Entry	R	M	Equiv. RM	Temp (°C)	Yield, **51** (%)
1	Me	MgCl	2	0	79
2	Et	MgBr	3	0	5
3	n-Pr	MgCl	2.2	0	11
4	n-Bu	MgCl	2	0	15
5	n-Bu	MgCl	1.5	22	35
6	n-Bu	Li	1.75	0	54
7	Ph	MgCl	1.6	0	30
8	Ph	Li	1.75	0	63
9	Bn	MgCl	1.85	0	43

compared to the Grignard reagents (compare entries 5 to 6 and 7 to 8). In the case of the less reactive Grignard reagents, higher yields were obtained at higher reaction temperatures (compare entries 4 and 5).

18. Synthesis of β-Trimethylsilyloxy Carbonyl Compounds

Palomo and co-workers[49] have explored an alternative methodology using N-methoxy-N-methylamides for the preparation of cross-aldol products in a regiocontrolled manner. Two different organometallic reagents were evaluated in this strategy. In one set of experiments, they found that α-bromo N-methoxy-N-methylacetamide reacted with carbonyl compounds in the presence of zinc powder and trimethylchlorosilane to furnish the β-siloxyamides **52** in good yields (Eq. 30). These

(30)

compounds were converted to the silyl protected aldol products **53** in the usual way by treatment with Grignard reagents (Table 6).

TABLE 6. Synthesis of β-Trimethylsilyloxy Carbonyl Compounds

Carbonyl Compound	M	Yield, **52** (%)	R^3	Yield, **53** (%)
Benzaldehyde	ZnBr	73	Methyl	81
Benzaldehyde	Li	82	4-Methoxyphenyl	73
4-Chlorobenzaldehyde	ZnBr	76	Ethyl	65
4-Chlorobenzaldehyde	Li	70		
2-Phenylpropionaldehyde	ZnBr	68	Allyl	76
2-Phenylpropionaldehyde	Li	70		
Cyclohexanone	Li	72	Methyl	70

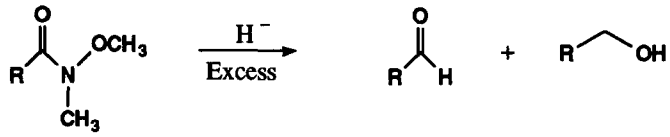
Alternatively, the lithium enolate prepared from the reaction of N-methoxy-N-methylacetamide and LDA underwent reactions with carbonyl compounds to produce the β-hydroxyamides. These compounds were silylated using triethylamine and chlorotrimethylsilane. One key feature of these experiments was that both enolizable and nonenolizable carbonyl compounds underwent reactions smoothly.

III. REDUCTIONS OF N-METHOXY-N-METHYLAMIDES

There are methods available for the direct conversion of carboxylic acid amides to aldehydes by the use of reducing agents.[50] However they are generally problematic. The reductions can follow different pathways to produce either the amine, the aldehyde, or the alcohol. The development of new methodologies for the selective reduction of carboxamide to aldehydes is thus very attractive.

1. Synthesis of Aldehydes

A well-utilized characteristic of the N-methoxy-N-methylamides is the conversion of this functional group to aldehydes under very mild conditions.[1] The underlying basis for the usefulness of N-methoxy-N-methylamides as an aldehyde equivalent is the formation of a stable chelated intermediate after hydride addition which prevents further additions, thus minimizing the amount of over reduced products. Several different reducing agents LAH,[1] LAD,[51] DIBAL-H,[1] and Red-Al[52] have been used for these reductions (Eq. 31 and Table 7).



(31)

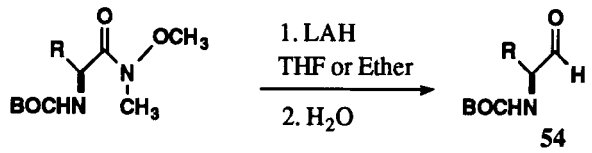
TABLE 7. Synthesis of Aldehydes by Reduction of N-Methoxy-N-methylamides

R	Reagent	Aldehyde, Yield (%)	Alcohol, Yield (%)
Ph	LAH	67	5
Ph	DIBAL-H	71	—
n-$C_{17}H_{35}$	LAH	50	25
n-$C_{17}H_{35}$	DIBAL-H	71	—
C_6H_{11}	DIBAL-H	74	—
Cinnamoyl	DIBAL-H	76	3
Cinnamoyl	LAH	70	14

Depending on the reaction conditions and the bulk of the reducing agent, one can obtain high selectivity in these reductions. Reductions with the bulkier reagent, DIBAL-H, proceed more selectively. The chemical yields in these reactions are high and typical workup procedures are employed, thus making the methodology a useful strategy for aldehyde synthesis.[53]

2. Synthesis of N-Protected α-Amino Aldehydes

N-protected α-amino aldehydes are important synthetic intermediates because of their widespread utility in the synthesis of biologically active amino alcohols and their derivatives.[54] An area where the N-methoxy-N-methylamide reduction chemistry has had a great impact is in the preparation of N-protected α-amino aldehydes. Castro and co-workers, in their first application of this methodology, showed that these reductions proceed without loss of optical purity when α-chiral N-methoxy-N-methylamides are employed as the substrates (Eq. 32).[55] There are a number of reports in the literature that illustrate the utility of this reduction strategy in the preparation of important synthetic intermediates in high optical purity.[56]

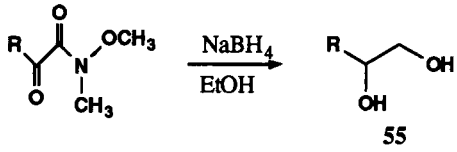


(32)

R	Yield, 54 (%)	R	Yield of 54 (%)
H_3C	88	$(H_3C)_2CH$	93
$H_3C(CH_3)CHCH_2$	96	$H_5C_6CH_2$	86
$H_3CCH_2(CH_3)CH$	90	$H_5C_6H_2CO(CH_3)CH$	95

3. Synthesis of 1,2-Diols

Sibi and Sharma[57] have reported an unprecedented mode of reduction for N-methoxy-N-methylamides where this functional group is converted to a primary alcohol under very mild conditions. Treatment of α-oxo-N-methoxy-N-methylamides with excess sodium borohydride at room temperature in ethanol furnished the corresponding 1,2-diols **55** in high yields (Eq. 33).

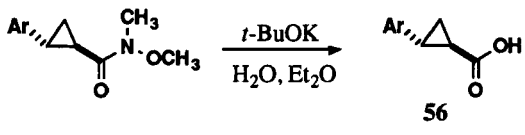


R	Yield, 55 (%)
Phenyl	92
p-Tolyl	89
p-Chlorophenyl	90
2-Furyl	80
2-Thienyl	90
Cyclohexyl	90
n-Butyl	84
n-Hexyl	81

(33)

IV. HYDROLYSIS OF N-METHOXY-N-METHYLAMIDES

Rodriques[19] has shown that N-methoxy-N-methylamides can be hydrolyzed to the corresponding carboxylic acids in high yields using the conditions developed by Gassman.[58] A series of cyclopropyl carboxylic acids **56** was prepared in this manner (Eq. 34).



R	Yield, 56 (%)
Phenyl	97
p-Bromophenyl	93
2-Naphthyl	100
3-Thienyl	97
5-Methyl-2-Furyl	90

(34)

V. CONCLUSIONS

This review has illustrated the versatility of the N-methoxy-N-methylamides. These amides are excellent carbonyl equivalents and have seen a large number of applications in a relatively short

time. The future holds promise for the extension of the utility of this functional group in a variety of synthetic transformations.

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