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Activation of α-sp^3 centres toward electrophilic substitution in alcohols and amines

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Abstract. The scope of electrophilic substitution at alpha-sp^3 centres in alcohols and amines via their alpha-lithio species is reviewed. The importance of alpha-activation by the hetero atom protecting group is deliniated with special reference to transient protection-activation methodology.

Keywords. Alpha-heterocarbanion; alpha-lithiation; protection; protection-activation; electrophilic substitution; alcohols; amines.

1. Introduction

Electrophilic substitutions at sp^3-carbons *alpha* to heteroatoms have created widespread interest from both synthetic and mechanistic viewpoints. However, such transformations demand the generation of α-heterocarbanions. This is a difficult proposition particularly for the many heteroatomic substrates (like alcohols and amines) which contain highly acidic protons attached to the heteroatom and require prior protection. Furthermore, the hydrogens *alpha* to heteroatoms are generally not acidic enough to be abstracted by even strong bases and activation of the α-carbon becomes necessary for proton removal. In addition to these problems, α-heterocarbanions face strong destabilizing interaction from the adjacent lone-pairs. Combination of the first two factors has led to the deployment of "protecting-activating agents" which, apart from protecting the heteroatomic centre, also activate the α-carbon toward proton loss. In rationalizing the stabilities of α-heterocarbanions, the concept of "dipole stabilization" has been invoked and nowadays this is regarded as the primary requirement for the generation of such species.

Since electrophilic substitution *alpha* to a heteroatom is a longstanding problem, not to mention the *umpolung* nature of such reactions, the current decade has seen extensive research activity in this area. As a result, several α-heterocarbanions (and synthons thereof) (Beak and Reitz 1978; Krief 1980; Beak *et al* 1984) derived from alcohols and from primary and secondary amines are now available.

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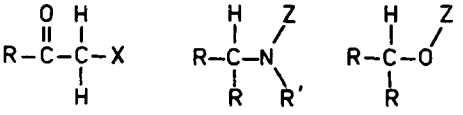
This review deals with the activation of α-sp^3 hybridized carbon atoms in amines and alcohols toward proton loss. In principle there are two distinct methods by which such activation may be achieved: (a) by the use of activating substituents directly attached to the carbon atom in question (e.g., **1** and **2**) or, (b) by the modification of the amino or the hydroxy group (see **3**, **4**). However, this review will only be concerned with the second type of activation, i.e., those depicted in (**3**) and (**4**).



(1); X = NR_2
(2); X = OR

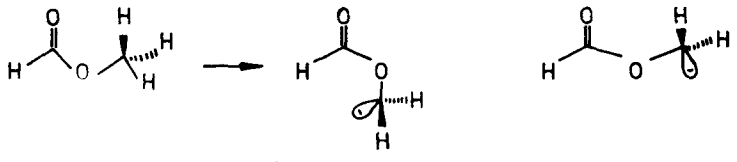
(3)

(4)

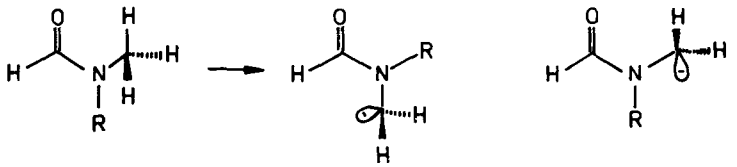
We first consider the secondary amines and the various types of Z-groups that can be utilized for the process of α-activation. Then primary amines and alcohols are each dealt with in a similar manner.

1.1 *Concept of dipole stabilization*

The commonly accepted theory behind dipole stabilization is shown below (figure 1) for α-carbanions to oxygen and nitrogen derived from the corresponding ester (**5**) and the amide (**7**), respectively.



(5) (6) - anti (6) - syn



(7) (8) - anti (8) - syn

Theoretical calculations (Rondan *et al* 1981; Al-Aseer *et al* 1983; Bach *et al* 1983) show that the carbanionic centres in **6** and **8** are pyramidal and the *anti* forms of both **6** and **8** are preferred over the *syn* forms, orientations which are exactly opposite to those of the parent ester (**5**) or the amide (**7**). this preferential *anti* orientation can be rationalized considering that only in this form do the internal dipoles suffer minimum repulsion. Even more convincing are the energy considerations which show that introduction of the formyl group in **6** and **8** provides 28 kcal/mole stabilization with respect to $^-CH_2OH$ and $^-CH_2NH_2$, respectively.

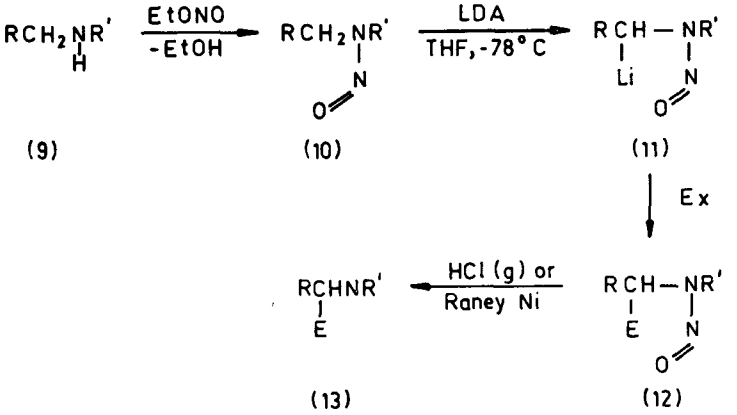
However, dipole stabilization has little or no contribution from resonance delocalization of the α-carbanions, an exception being the α-carbanions derived from N-nitrosoamines. In the latter cases, it is the resonance stabilization of the α-carbanion and not the dipole formation which is responsible for the α-deprotonation (Fraser and Ng 1976).

2. α-Activation of secondary amines

α-Activation of secondary amines toward deprotonation has been achieved *via* several synthons (Beak and Reitz 1978; Beak *et al* 1984). Some significant ones are described below, for space limitations do not allow an exhaustive survey.

2.1 *Nitrosoamines*

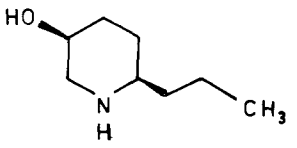
The use of the nitroso group for α-activation of secondary amines, developed by Seebach (Seebach and Enders 1975), has been reviewed (Saavedra 1987). In this process, a secondary amine (**9**) is first transformed into its N-nitroso derivative (**10**) by nitroso transfer from ethyl nitrite. Treatment of **10**, at low temperatures, with LDA affords the α-lithio species (**11**) which can be trapped with a suitable electrophile to produce the α-substituted nitrosamine **12**. A wide range of electrophiles including alkyl halides, carbonyl compounds and sulphur, tin and silicon electrophiles give moderate to good yields of the products (**12**). After serving its purpose, the nitroso group can be removed from 12 either by gaseous HCl or by Raney-Nickel both of which liberate the α-substituted secondary amine (**13**) (scheme 1).



Scheme 1.

A particularly attractive feature of the nitrosoamines is their ability to afford α-deprotonation of primary, secondary and even tertiary hydrogens. This remains unattainable by other systems except for the formamidines (*vide infra*). In unsymmetrical nitrosoamines, the regiochemistry of carbanion formation is guided by both kinetic and thermodynamic factors. Thus nitrosoamines usually undergo kinetic α-metallation on the least substituted carbon (Seebach and Enders 1975; Saavedra 1987) and there are evidences showing that the carbon *syn* to the

nitroso-oxygen undergoes preferential proton abstraction (Barton *et al* 1975). However, in presence of anion stabilizing groups (*e.g.*, phenyl) at the α-position, thermodynamic stabilization of the carbanion competes with kinetic deprotonation (Seebach and Enders 1975; Saavedra 1987). In cyclic systems such as N-nitrosopiperidine derivatives, the sequence of α-metallation and alkylation usually affords axial products; this is a direct consequence of kinetically controlled α-metallation (Fraser and Ng 1976; Renger *et al* 1977) giving rise to the axial α-lithio species. This stereochemical bias was elegantly exploited in the syntheses of piperidine alkaloid, ψ-conhydrine (**14**) (Enders *et al* 1976), and the pyrrolidine alkaloid (**15**) (Fraser and Passannanti 1976), the latter being a constituent of the fire ant defence system. Further important uses of α-lithionitrosoamines include their conversion to amino acids (CO_2 as electrophile (Fraser *et al* 1975) as well as to triazoles (with nitrile electrophiles) (Seebach *et al* 1977). Recently, enantioselective alkylation of α-lithionitrosoamines was attempted in chiral reaction media but resulted in low optical yields (e.e. 25%) (Seebach and Greiss 1976; Soai and Mukaiyama 1979).



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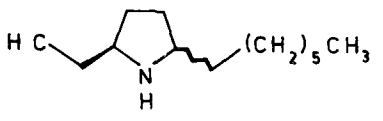


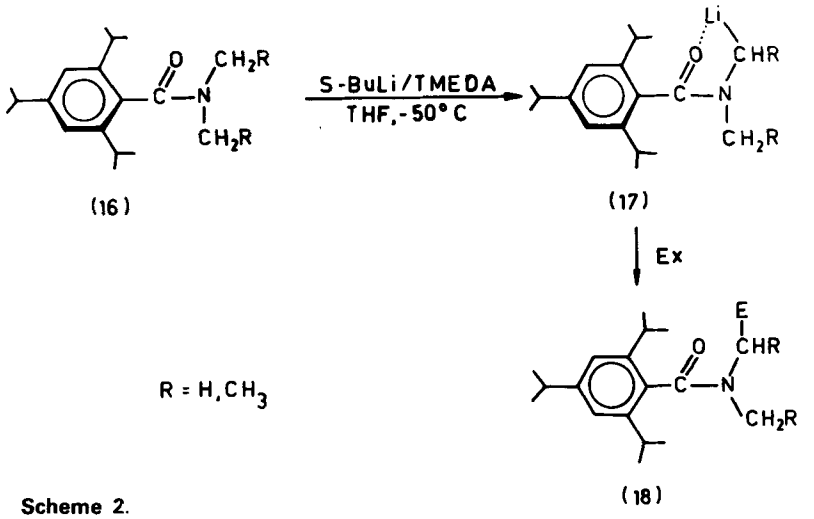
(15)

However, nitrosoamines suffer heavily from the handling hazards involved since these compounds are potent carcinogens and/or mutagens. Although a one-pot procedure for the overall transformation is now available (Seebach and Wykypiel 1979) their high toxicity has considerably limited their use as α-aminocarbanion synthons.

2.2 *Amides*

α-Activation of secondary amines *via* their amides has been extensively investigated by Beak and co-workers (Beak and Reitz 1978; Beak *et al* 1984). It is well known that amides themselves are potent electrophiles and proper structural modifications were necessary to direct the metallating agent to the α-carbon. This was achieved by using the 2,4,6-triisopropylbenzamide derivative (**16**) where the carbonyl group is sterically protected from attack by any nucleophile. Such amides undergo α-lithiation with *s*-BuLi/TMEDA giving rise to the dipole-stabilized carbanions **17** which can be trapped at least with some electrophiles in good yields (scheme 2). Of particular interest is the fact that the *ortho*-substituents in **16** impose substantial rotational barrier to the N–C bond so that metallation occur only on the carbon *syn* to the carbonyl oxygen (Schlecker *et al* 1978, Beak and Meyers 1986) (scheme 2).

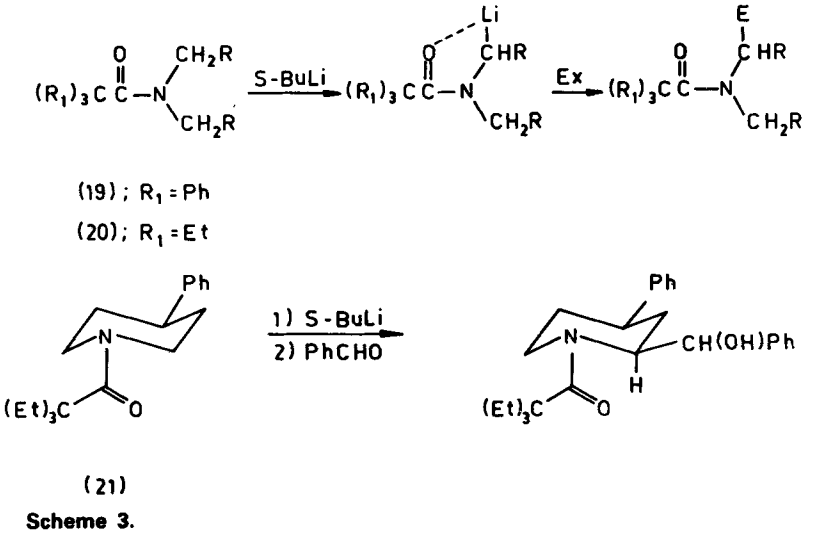
Other hindered acyl systems, such as those in triphenylacetamides (**19**) (Wykypiel *et al* 1981) and triethylacetamides (**20**) (Reitz *et al* 1981; Beak and Zajdel 1984), have also found use as α-activating agents for dimethyl- and diethylamines (scheme 3). In addition, the triethylacetamides can also be used for cyclic secondary amines such as piperidine and pyrrolidine. The piperidine-derived compound **21**, in contrast to N-nitrosopiperidine (*vide supra*), affords preferential



(16) (17) (18)

Scheme 2.

equatorial substitution which has been explained on the basis of *syn*-metallation aided by prior complexation of the lithiating agent with the carbonyl oxygen (Al-Aseer *et al* 1983).



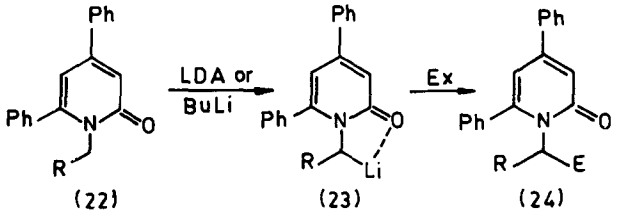
(21)

Scheme 3.

The principal disadvantage of using hindered amides as α-aminocarbanion synthons stems from the very harsh deprotection conditions. For example, the triphenylacetamides require dissolving metal reduction for deprotection whereas hydrolytic cleavage of the triisopropylbenzamides has failed completely.

1-Alkyl-2-pyridones (**22**) form an interesting class of cyclic amides which also undergo α-metallation with alkyllithiums and LDA. In our laboratory, it has been shown, (Katritzky *et al* 1980a, b, 1982, 1983) that the derived dipole-stabilized α-carbanions (**23**) can be alkylated under judicious choice of reaction conditions (scheme 4). However, α-carbanions from 2-pyridones are highly unstable and tend to undergo dimerization (Patel and Joule 1985) and other side reactions. This problem has recently been solved by utilizing 1-trimethylsilylmethyl-2-pyridone,

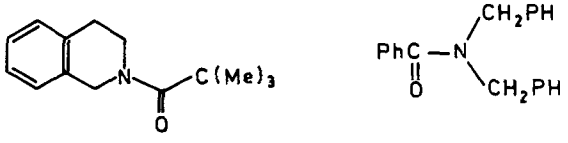
the F^- catalyzed desilylative hydroxyalkylation and acylation of which occur under essentially neutral conditions with no side reactions (Katritzky and Sengupta 1987b).



(22) (23) (24)

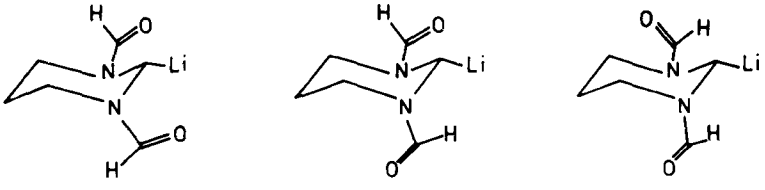
Scheme 4.

There are numerous examples of α-lithiation of amides derived from secondary amines possessing carbanion-stabilizing α-substituents, *e.g.*, those derived from tetrahydroisoquinoline (**25**) (Lohmann *et al* 1981, 1983) and dibenzylamine (**26**) (Fraser *et al* 1973).



(25) (26)

However, α-activation by an amide may not necessarily be additive. MNDO calculations on the *bis*-formamides (**27**) show that the equatorial *syn-syn* conformer (**27a**), as expected (Rondan *et al* 1981; Al-Aseer *et al* 1983; Bach *et al* 1983), is more stable than the equatorial *syn-anti* conformer (**27b**) due to the double O-Li coordination present in the former. However, this difference is considerably less than that between **27b** and the least stable *anti-anti* conformer (**27c**) (Katritzky *et al* 1987b). Supporting these calculations is the fact that α-carbanions derived from diacylimidazolidines and diacylhexahydropyrimidines, although they can be trapped with MeI or D_2O, show strong tendencies toward self-condensation (Murugan 1987).

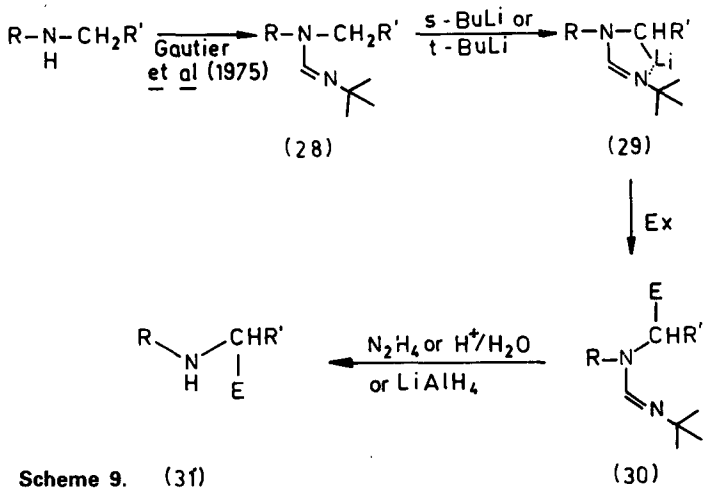


(27a) (27b) (27c)

2.3 *Formamidines*

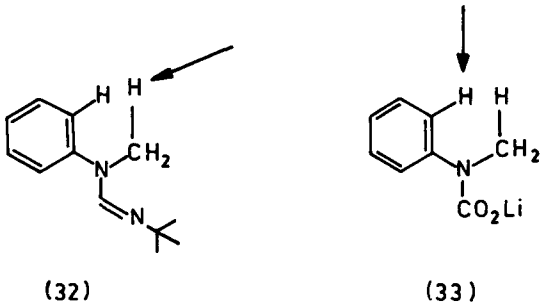
In recent years, extensive work by Meyers and co-workers (Meyers 1985) has established the formamidine group as the most versatile α-activating group for

secondary amines. Secondary amines can be transformed into the corresponding formamidines (**28**) by various established methods (Gautier *et al* 1975). α-Lithiation can be achieved with *s*- or *t*-BuLi to give the dipole-stabilized α-carbanion (**29**) which reacts with alkyl halides, aldehydes and ketones forming the α-substituted amidines (**30**) in good yields. Unlike the amides, the formamidines can be deprotected with relative ease (acid hydrolysis, hydrazinolysis, or by $LiAlH_4$) to unmask the α-substituted secondary amine (**31**) (scheme 9). This methodology enables α-lithiation on primary, secondary, as well as tertiary centres, and embraces a wide range of secondary amines, notable among which are tetrahydroisoquinoline (Meyers *et al* 1981), tetrahydroquinoline and indoline (Meyers and Hellring 1981), alicyclic amines (piperidine, pyrrolidine, hexahydroazepine, etc.) (Meyers *et al* 1984b) and β-carboline (Meyers and Hellring 1982).



Scheme 9.

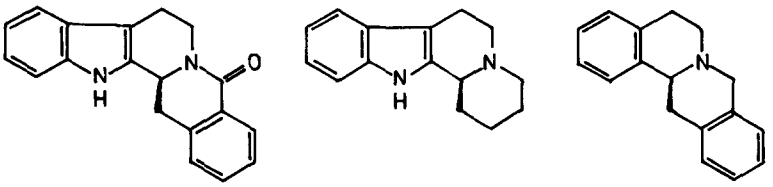
The α-activating and directional ability of the formamidines was clearly demonstrated by metallation studies on the formamidine **32** derived from N-methylaniline. The metallation took place exclusively on the methyl group (Meyers and Hellring 1981). This result is quite significant in view of the alternative lithiation sites (*ortho* lithiation) in the molecule. Recently, our group has shown (Katritzky *et al* 1986) that N-alkylanilines indeed undergo *ortho*-lithiation *via* their lithium carbamates (**33**) which indirectly proves the effectiveness of the formamidines.



(32) (33)

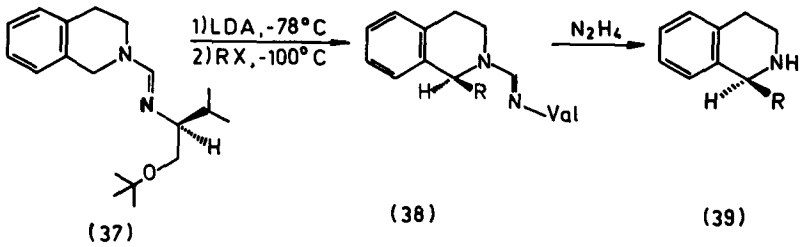
A further point of interest is that in a conformationally stable system such as 4-*t*-butylpiperidine, α-alkylation *via* the formamidine method gives the equatorial or the *cis* product (Meyers *et al* 1984b). As in the case of that for the amides (*vide supra*), this result can be rationalized by the intermediacy of an equatorial α-lithio species which undergoes alkylation with retention of configuration (Rondan *et al* 1981; Al-Aseer *et al* 1983; Bach *et al* 1983). It is only in this conformation that the C–Li bond remains orthogonal to the π-system of the formamidine, an orientation which has been established as the one preferred by dipole-stabilized carbanions.

The synthetic potential of the formamidine method is best appreciated from its application to the synthesis of several skeletons common to naturally occurring alkaloids. Significant achievements include the yohimbane skeleton **34** (Meyers and Hellring 1982) and the indolo [*b*] quinolizidine **35** (Meyers and Loewe 1984), both derived from β-carboline, and the dibenzoquinolizidine **36** (Meyers *et al* 1981) prepared from tetrahydroisoquinoline (bold bonds show the point of α-alkylation).



(34) (35) (36)

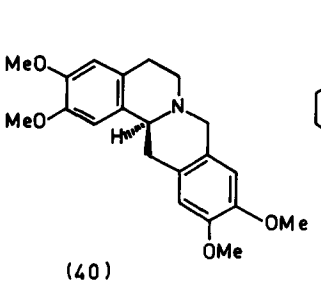
The most significant property of the formamidines is their ability to take part in asymmetric α-alkylation (Loewe *et al* 1985; Gawley 1987; Meyers and Dickman 1987). The chiral formamidine (**37**), derived from tetrahydroisoquinoline and *L*-valinol *t*-butyl ether, when treated with LDA followed by addition of alkyl halides and hydrazinolysis gave rise to the 1-substituted tetrahydroisoquinolines (**39**) in greater than 90% enantiomeric excesses (scheme 10) (Meyers *et al* 1984a).



(37) (38) (39)

Scheme 10.

Isoquinoline alkaloids (−)−salsolidine, (−)−norcoralydine (**40**) and (+)−homolaudanosine gave way to this efficient methodology and greater than 95% enantiomeric excesses (with the correct absolute configuration) were obtained in each case (Meyers *et al* 1984a). β-Carboline *via* its chiral formamidine also undergoes asymmetric alkylation and the naturally occurring indoloquinolizine (**41**) was prepared in 95% e.e. (Loewe and Meyers 1985). Other alkaloids which have been synthesized from chiral formamidines in high (>95%) optical purities are (+)−ocoteine (Dickman and Meyers 1986), dextrorphan (**42**) (Meyers and Bailey 1986), (−)−deplancheine (Meyers *et al* 1986), and the antibiotic (+)−anisomycine (**43**) (Meyers and Dupre 1987).



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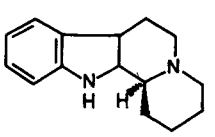

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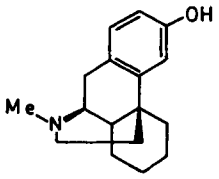

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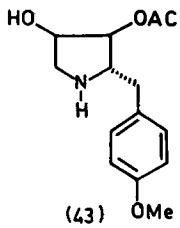
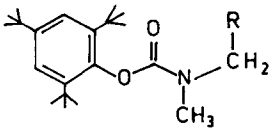


(43)

Unfortunately chiral formamidines fail in those cases for which the α-proton is not benzylic or allylic (Meyers *et al* 1985). Chiral oxazolines have been employed instead for unactivated systems such as piperidine but with very limited success (Gawley *et al* 1986).

2.4 *Neutral carbamates*

Alkyl-/aryl-oxycarbonyls are less efficient α-activating groups than acyls. This is primarily due to the greater susceptibility of the carbamates toward nucleophilic attack; strong bases like alkyllithiums are not compatible with carbamates. Nevertheless, Seebach has shown that the 2,4,6-tri-*t*-butylphenoxy moiety provides sufficient steric protection of the carbonyl group in **44** so as to generate the corresponding α-lithio species **45** with *s*-BuLi (Seebach and Hassel 1978); however, this steric factor prevents subsequent deprotection of the carbamate and the sequence becomes preparatively unattractive. On the other hand, activated systems such as allyl amines can be α-lithiated (with LDA) *via* their alkyl carbamates. This procedure has led to elegant syntheses of some indolizidine and pyrrolizidine alkaloids (Lapiere Armande and Pandit 1977; Macdonald 1980; Macdonald and Narayanan 1983).



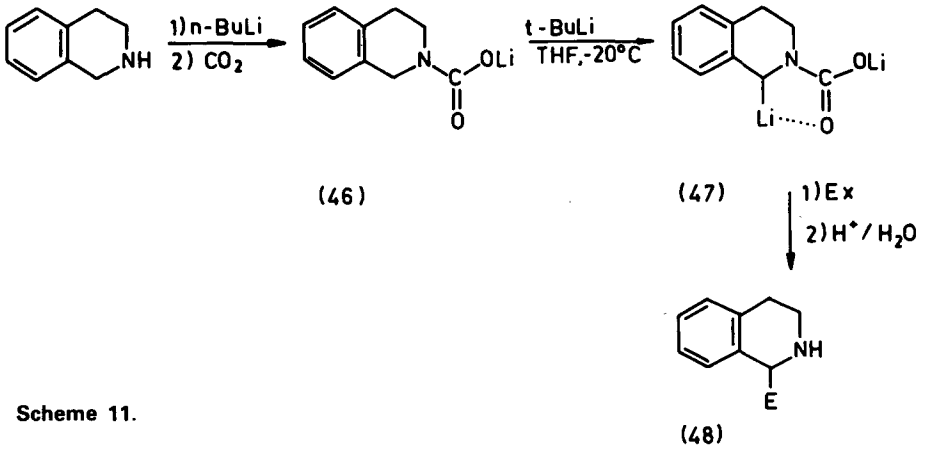
44) R = H

45) R = Li

2.5 *Carbamate anions*

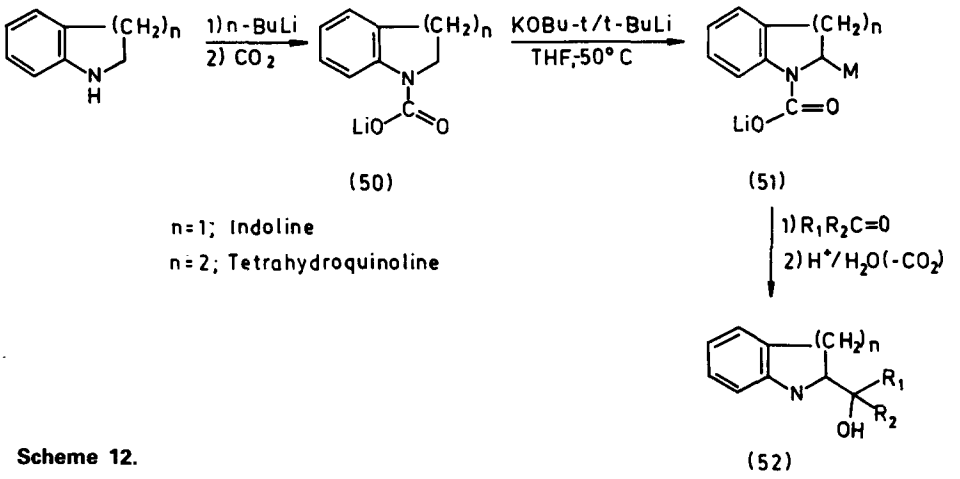
A recent advancement in this class involves transient activation of secondary amines *via* anionic protection. In our laboratory, this concept has allowed the use of carbon dioxide as a protecting-activating group for secondary amines, among various other heteroatomic substrates. As an example, tetrahydroisoquinoline can be easily converted to its lithium carbamate (**46**). On treatment with *t*-BuLi, the lithium carbamate derivative smoothly generated the 1-lithio species (**47**) which could be trapped with a wide range of electrophiles. Acidic work-up brings about spontaneous deprotection (loss of CO_2) and the 1-substituted tetrahydroisoquino-

lines (**48**) are obtained in good yields (scheme 11) (Katritzky and Akutagawa 1986). As none of the intermediates needs isolation, the whole sequence can be performed in the same reaction vessel. This procedure presently offers the easiest route for electrophilic substitution at the 1-position of tetrahydroisoquinoline.



Scheme 11.

Lithium carbamates are less activating for α-lithiation in unactivated systems. Thus *t*-BuLi alone fails to α-lithiate the tetrahydroquinoline- or piperidine-derived lithium carbamates. However, a combinanation of $KOBu^t$ and *t*-BuLi in THF, a stronger metallating system, successfully α-metallates the lithium carbamates (**50**) of tetrahydroquinoline and indoline, and the corresponding α-metallo species (**51**) (presumed to be a α-potassio species) can be trapped with carbonyl electrophiles (PhCHO, Ph_2CO, cyclohexanone). Acidic work-up effects spontaneous liberation of CO_2 to afford the α-substituted products (**52**) in 50–70% yields, again in a *one-pot* sequence (scheme 12) (Katritzky and Sengupta 1988). However, poor yields (*ca.* 15%) were obtained (Katritzky and Sengupta, unpublished) when this sequence was applied to piperidine. This is probably due to the unstable nature of the α-piperidyl carbanion (Meyers *et al* 1984b).

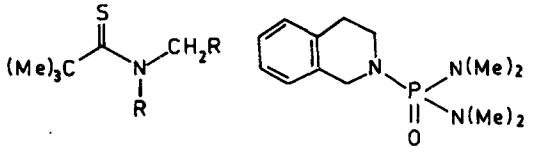


Scheme 12.

The lithium carbamate route offers several advantages. The substrates are relatively inert to nucleophilic attack and introduction of the CO_2 protecting group as well as its removal can be achieved under very mild conditions. Thus an overall *one-pot* conversion of secondary amines to the α-substituted products can be easily carried out.

2.6 *Others*

Various other α-activating groups for secondary amines have been recorded in the literature (Beak and Reitz 1978; Krief 1980; Beak *et al* 1984). Among them the thiopivalamides (**53**) are quite effective for α-lithiation of acyclic secondary amines. They can be either hydrolyzed to the secondary amines or reduced to the neopentyl tertiary amines depending on the conditions of deprotection (Lubosch and Seebach 1980). α-Lithiation of phosphoramides may represent a useful process since their hydrolysis to the secondary amines is relatively easy. Hexamethylphosphoric triamide (HMPA), a common additive in lithiation processes, has been successfully α-lithiated (Savignac *et al* 1975; Magnus and Roy 1980).



(53) (54)

Quite significant is the synthetic potential of the tetrahydroisoquinoline-derived phosphoramide **54** which can be lithiated at the 1-position and subsequently alkylated with a wide variety of electrophiles (Seebach and Yoshifuji 1981). However, phosphoramides do not provide strong α-activation and the presence of additional α-activating groups is essential for success.

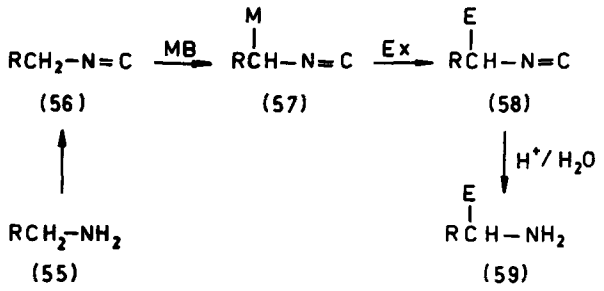
3. α-Activation of primary amines

α-Activation of primary amines toward electrophilic substitution is a difficult task because of the presence of two amino-protons, both of which need protection. In recent years many α-metallo primary amine synthons have been developed. However, their wide variety precludes a systematic classification. Some of those which are preparatively useful have been chosen for this review. A list of possible α-aminocarbanion synthons is given in Seebach and Enders (1975).

3.1 *Isonitriles*

α-Metallated isonitriles (or isocyanides) have a wide range of synthetic applications and several reviews have already appeared on these topics (Schoellkopf 1970, 1977, 1979; Hoppe 1974). Hence, only an essence of this methodology will be presented here. It should be noted that various bases (BuLi, LDA, $KOBu^t$, NaH, etc.) can be used for α-deprotonation of isonitriles, the choice depending on the nature of the substrate.

Extensive studies by Schoellkopf and co-workers have shown that isonitriles (**56**) can be α-lithiated with BuLi and the resulting α-lithio species (**57**) reacts with various electrophiles to give the α-substituted isonitriles in good yields (scheme 13). Particular care should be taken during the α-lithiation step since organolithium reagents can add across the N=C bond of isonitriles to give the corresponding lithio aldimines (Hirowatari and Walborsky 1974; Niznik and Walborsky 1974; Niznik *et al* 1984; Periasamy and Walborsky 1974). To avoid such undesired reactions, the use of less nucleophilic bases such as lithium 2,2,6,6-tetramethylpiperimide has been recommended. *sec*-Alkyl isonitriles are not easily α-metallated unless the α-position is additionally activated by anion-stabilizing groups, a notable exception being the cyclopropyl isonitrile (Schoellkopf *et al* 1977; Harms *et al* 1978). The α-anion from the latter can be generated with BuLi and serves as a useful synthon for the (otherwise difficult to prepare) cyclopropyl amines. In scheme 13, the α-lithio species (**57**) reacts with a wide range of electrophiles, such as carbonyl electrophiles (including α, β-unsaturated systems) (Schoellkopf 1970, 1977, 1979; Hoppe 1974), epoxides (Schoellkopf and Jentsch 1973) (to give γ-amino alcohols), carbonic esters (Matsumoto *et al* 1973) (to give amino acid derivatives), etc. Since primary amines can be easily converted to the corresponding isonitriles and *vice versa* (Ugi 1971), the above procedure constitutes an excellent method for α-alkylation of primary amines. Isonitriles with leaving groups at the α-position constitute a special class of synthons of which *p*-tosylmethyl isocyanide (TosMIC) (Possel and van Leusen 1977; Saikachi *et al* 1979; van Nispen *et al* 1982) has found wide synthetic applications.

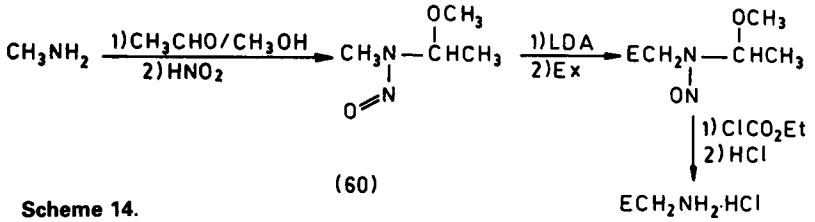


Scheme 13.

The mechanism of α-activation in isonitriles is, however, not clear. Walborsky (Walborsky and Periasamy 1974; Periasamy and Walborsky 1977) showed that (+)–(S)–1–isocyano-2,2-diphenylcyclopropyl lithium is configurationally stable below −50°C. From this it was inferred that the α-carbanion is not resonance-stabilized and this evidence points toward dipole stabilization (Beak and Farney 1973).

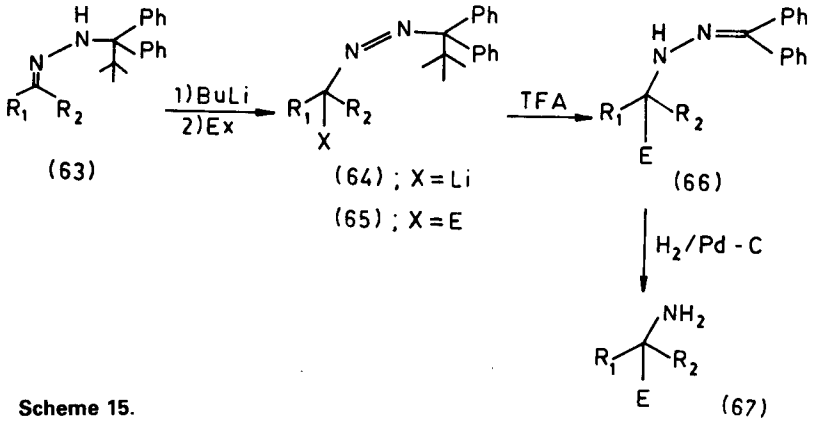
3.2 *Others*

A few other primary α-lithio amine synthons have recently appeared. Of these the most promising is the α-(nitrosoamino)alkyl ether (**60**) (Saavedra 1983). This interesting synthon gives, upon α-metallation followed by reaction with electrophile and hydrolysis, the α-substituted primary amines in useful yields (scheme 14).



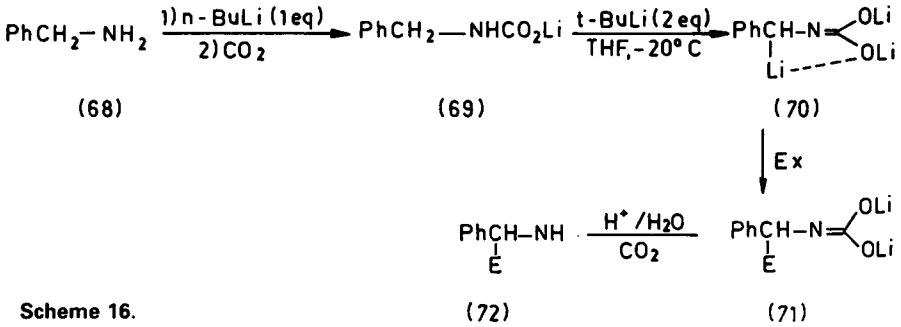
Scheme 14.

Another approach involves the α-metallation of the *t*-butyldiphenylmethyl hydrazones (**63**) (Baldwin *et al* 1986); the resulting α-lithio species (**64**), upon alkylation followed by deprotection (by sequential treatment with trifluoroacetic acid and H_2/Pd-C), produces the α-substituted primary amines (**68**) (scheme 15).



Scheme 15.

Additional α-activation as in benzylamine makes the task of α-lithiation much easier. Tischler and Tischler (1978a) have shown that N-benzylbenzamide can be α-lithiated when treated with two equivalents of BuLi and the derived α-lithio species reacted with electrophiles to give α-substituted N-benzylbenzamides. Hydrolysis of the latter completes a three-step procedure for α-alkylation of benzylamines. In a significant improvement over the above procedure, we have recently described (Katritzky *et al* 1987a) the use of CO_2 as a protecting group during α-lithiation of benzylamine. In this method, benzylamine was first converted to its lithium carbamate (**69**) which upon α-lithiation with *t*-BuLi (2 eq.) followed by electrophilic substitution and acidic work-up afforded the α-substituted benzylamines (**72**) in a one-pot sequence (sequence 16).



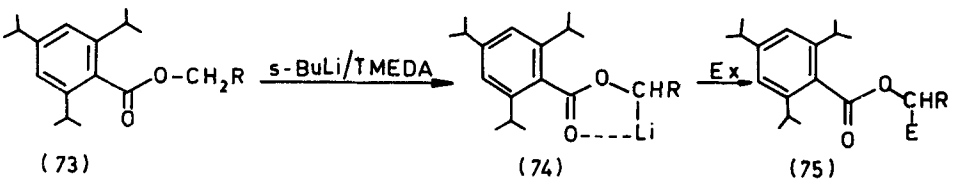
Scheme 16.

Tischler and Tischler (1978b) have also investigated other primary amide derivatives which are capable of α-lithiation. From that study it may be inferred that unless additional α-activating substituents are present, the α-lithiation of primary amides is virtually impossible.

4. α-Activation of alcohols

Among all the heteroatomic systems, α-hydroxycarbanions are most difficult to generate; also, once generated they undergo facile 1,2-anionic migrations, thus limiting their synthetic potential. These difficulties are reflected by the dearth of α-hydroxycarbanion synthons in the literature.

Beak and McKinnie (1977) were the first to generate a diopole-stabilized α-hydroxycarbanion equivalent (**74**) *via* α-lithiation (*s*-BuLi/TMEDA) of the hindered ester (**73**) (scheme 17). Here, steric hindrance protects the carbonyl group from nucleophilic attack and directs the lithiating base onto the α-carbon. Although **74** can be reacted with electrophiles to give the α-substituted ester (**75**), hydrolytic deprotection of the latter is difficult. The desired α-substituted alcohol (**76**) can be liberated from **75** only if very drastic conditions ($LiAlH_4$ in refluxing THF) are applied. Similar results were also obtained by Seebach using methyl 2,4,6-tri-*t*-butylbenzoate (Schlecker *et al* 1978).



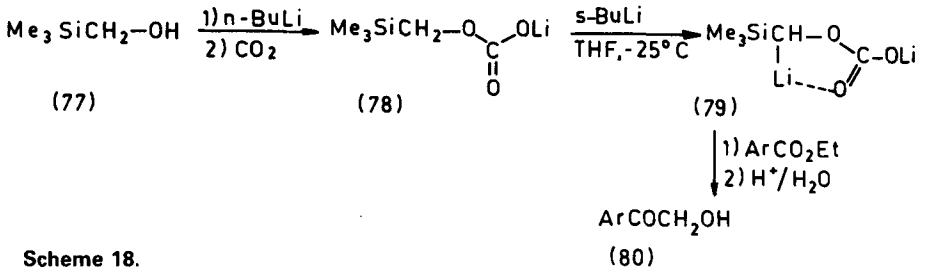
(73) (74) (75) (76)

Scheme 17.

In a novel approach, we have recently reported (Katritzky and Sengupta 1987a) the use of trimethylsilyl group as an easily removable α-activating auxiliary. This led to the successful utilization of 1-trimethylsilylmethanol (**77**) as a methanol dianion synthon in a one-pot sequence. The lithium carbonate (**78**), upon treatment with *s*-BuLi, generated the α-lithio species (**79**) which upon reaction with an ester followed by acidic work-up directly afforded the α-hydroxy ketone (**80**) (scheme 18).

α-Lithiation of alcohols is much easier when an additional activating group is present at the α-position. α-Metallation of various allyloxy derivatives and their use as homo-enolate equivalents has recently been reviewed (Hoppe 1984).

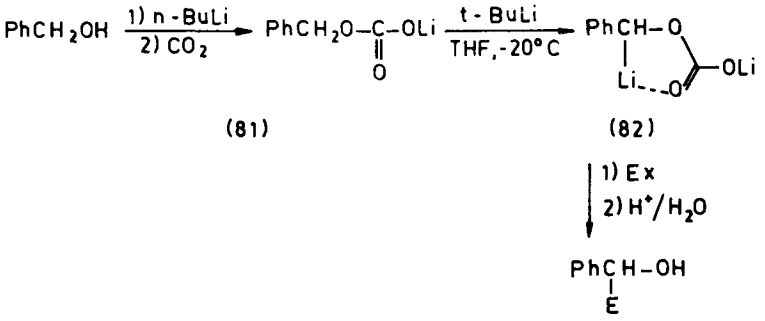
α-Lithiation studies of benzyl alcohol provide an interesting scenario. First is the report (Meyer and Seebach 1978, 1980) that benzyl alcohol undergoes alkoxide-directed *ortho*-lithiation when treated with two equivalents of *n*-BuLi. On the other



(77) (78) (79) (80)

Scheme 18.

hand, if the hydroxy is protected as its silyl ether, the α-carbanion can be easily generated with *t*-BuLi; however, such α-carbanions are unstable and rapidly rearrange to α-silylbenzyl alcohols (Wright and West 1974). In our laboratory, the use of CO_2 protecting group has provided a means by which α-lithiation of benzyl alcohol can be achieved. This method is devoid of the above complications. Thus, the benzyl alcohol-derived lithium carbonate (**81**), when treated with *t*-BuLi, underwent facile α-lithiation, and the resulting α-lithio species (**82**) was trapped with a number of electrophiles (Katritzky *et al* 1987a). Deprotection occurred spontaneously in the acidic work-up stage to afford the α-substituted benzyl alcohol (**83**) in an overall one-pot procedure (scheme 19).



(81) (82) (83)

Scheme 19.

5. Summary

A general outline for electrophilic substitution at the α-position of alcohols and amines *via* their α-metallo species has been attempted in this review. It is by no means an exhaustive coverage and interested readers are urged to refer to the other reviews (Seebach and Enders 1975; Beak and Reitz 1978; Krief 1980; Beak *et al* 1984; Meyers 1985) on this topic. During the past few years, the field of α-hetero organometallics has developed rapidly, and the generation of α-metallo secondary amines has received the most attention. Our own contribution in this field is the concept of transient activation using carbon dioxide as the protecting-activating group. This has led to the generation of α-lithio-alcohols and -amines (both primary and secondary) in a one-pot sequence. Further research on α-hetero organometallics should continue now that it is known that these species are indeed viable targets should give greater emphasis to the search for simpler methods for their generation. In this respect, "transient activation" appears to hold much promise.

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