82. Togo, H.; Iida, S. Synlett 2006, 2159.
CHAPTER 2

Study on Lewis acid catalyzed N-alkylation reactions: Iodine catalyzed N-alkylation

Part-1

N-Alkylation reactions in organic synthesis
2.1.1. Introduction:

N-Alkyl amine is one of the key functional groups in organic chemistry.\textsuperscript{1} The development of a new methodology for the formation of carbon-nitrogen bonds is a challenging area of organic synthesis. N-Alkylation reactions have attracted significant attention because N-alkylated products exhibit a wide range of biological activities such as antibacterial, anticancer, antiviral functions, and HIV protease inhibitors.\textsuperscript{2} N-Alkyl amines are typically synthesized by using conventional alkylating agents, such as alkyl halides, alkyl or aryl alcohols in presence of Lewis acid catalysts. There are many Lewis acids that have been used as efficient catalysts for the synthesis of N-alkyl amines.

Alkyl amines are an important class of compounds in bulk chemistry and also serve as important intermediates in organic synthesis. One example is ethylamine, which is the single most commercially important alkyl amine and accounts for about 35% to 40% of the world’s annual requirement for alkyl amines.\textsuperscript{3} Basic amines derived from natural sources were traditionally known as “vegetable alkalis”, but they are now known as alkaloids.\textsuperscript{4} Their basic nature gives rise to often potent physiological activities. Some representative alkaloids include caffeine, nicotine and quinine shown in Figure 2.1.

![Figure 2.1: Structures of some representative alkaloids](image-url)
A large number of medicinally and biologically important N-alkylated compounds owe their activities to the presence of amino groups. Many possess powerful physiological activities and others have been associated with a wide range of biological applications such as use as antidepressants, neurotransmitters and antihistamines. Venlafaxine (Effexor) has an amino functional group and was the 13th best selling prescription drug in 2007. It is prescribed for the treatment of clinical depression and anxiety disorders. Antergan was the first antihistamine to be used in man in 1942, while Tripelennamine, a classic antihistamine structurally similar to Antergan is still in use today to treat asthma, hay fever, rhinitis and urticaria. Another prescribed drug is Chlorpheniramine (commonly marketed as Piriton) commonly used to prevent symptoms of allergic conditions and dopamine is an important neurotransmitter in the brain (Fig 2.2). Abnormalities in the level of dopamine in the brain are associated with many psychiatric disorders such as Parkinson’s disease.

![Chemical structures](image)

**Figure 2.2: Some medicinally important amines**
It is interesting to note that a common structural feature found in many medicinal drugs or biologically important compounds is the 2-phenylethananime (β-phenethylamine) unit (Figure-2.2). The structural similarities of these compounds could be related to their physiological and psychological effects. This unit appears to be crucial for the binding to brain receptor sites responsible for neurotransmitter action at certain nerve terminals that either control appetite and muscular activity or euphoric stimulation.

N-Alkylated amines are also useful intermediates in the preparation of solvents, fine chemicals, cosmetics and azo dyes. Another major application of amines is in the agrochemical industry. Some agrochemicals are pure amines, such as the herbicides based on pyridine, triazine or phenylene diamine, but an amide-based or urea-based agrochemical is often used which then gets metabolised to an amine. Generally, amines and tertiary amines, in particular, are some of the most common structural features of naturally occurring biologically active compounds as well as they are being important intermediates in the chemical industry.

2.1.2. Review of literature

Many methods have been reported in literature for the N-alkylation of amines, in which Lewis acids are used as efficient catalysts.

N-Alkylated amines are conventionally synthesised by the alkylation of alkyl halides with ammonia or amines but over-alkylations are common leading to mixtures of primary, secondary, tertiary amines as well as quaternary ammonium salts (Scheme 2.1).

![Scheme 2.1](image-url)

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64
Nakama et al. (2001)\textsuperscript{12}: In the presence of Lewis acid catalysts, aldoximes react with α, β-unsaturated carbonyl compounds at room temperature to give N-alkynitrone in good yields. Combination of two Lewis acid catalysts, zinc(II) iodide/boron trifluoride etherate (50 mol%/50 mol%), is the best choice to mediate the reactions producing N-alkylated nitrones in excellent yields.

\[
\begin{align*}
\text{RCH=NOH} & \quad + \quad \text{\textsubscript{\textit{X}}C=C} \quad \rightarrow \quad \text{\textsubscript{\textit{R}}} \text{\textsubscript{\textit{X}}} \text{\textsubscript{\textit{O}}} \text{\textsubscript{\textit{N}}} \text{\textsubscript{\textit{X}}} \\
\text{R=} & \text{Ph, Alkyl, X=} \text{Me, OMe, H}
\end{align*}
\]

\text{Scheme 2.2}

Jinling He et al. (2010)\textsuperscript{13}: The N-alkylation of primary amines and ammonia (in situ generated from urea or aqueous ammonia) with alcohols to secondary amines was efficiently promoted by supported copper hydroxide catalysts, Cu(OH)$_2$/Al$_2$O$_3$ and Cu(OH)$_2$/TiO$_2$.

\[
\begin{align*}
n\text{C}_7\text{H}_15\text{NH}_2 & \quad + \quad \text{PhOH} \quad \rightarrow \quad n\text{C}_7\text{H}_15\text{NHPh} & \quad + \quad n\text{C}_7\text{H}_15\text{NPh} \\
\text{Cat=} & \text{Cu(OH)$_2$/Al$_2$O$_3$, Cu(OH)$_2$/TiO$_2$}
\end{align*}
\]

\text{Scheme 2.3}

Jiayan et al. (2012)\textsuperscript{14}: TiCl$_4$–mediated intermolecular or intramolecular direct N-alkylation reaction of sulfonamides with inactive ethers as alkylating agents was successfully achieved, and the effects of sulfonamide substrate, the kinds of Lewis acid, solvents, reaction time and reaction temperature etc. on the N-alkylation were systematically investigated. This method provides a novel approach to make N-alkylsulfonamides from inactive ethers via an easy work-up procedure and this is the first report on the N-alkylation of sulfonamides using inactive ethers as alkylating reagents.
Bhattacharyya et al. (1994)\textsuperscript{15}: The combination of sodium borohydride with titanium isopropoxide described by Bhattacharyya offers a mild and efficient one-pot reagent system in the reductive amination of formaldehyde with primary and secondary amines.

Bhattacharyya et al. (1995)\textsuperscript{16}: A mixture of dimethylamine hydrochloride and triethylamine is used as the source of dimethylamine. The reaction is thought to proceed through the formation of titanium(IV) complex as an intermediate which is reduced either directly or via a transient iminium species. The reaction conditions are also compatible with reducible and acid-sensitive functional groups including acetonide, tert-butylimethylsilyl ether and acetals. However, this system needs titanium(IV) isopropoxide as a Lewis acid and requires long reaction times.
Varma et al. (2004)\textsuperscript{17}: A direct method for the generation of unfunctionalised tertiary amines via a microwave-assisted N-alkylation of primary or secondary amines by alkyl halides in aqueous media has been developed. By this method, tertiary amines including cyclic amines were synthesized with good to excellent yields. This method is atom-efficient, but requires the use of specialized microwave equipment and is not applicable to large scale preparation. The use of a strong inorganic base in stoichiometric amounts could again potentially harm base-sensitive functional groups.

Mohri et al. (1995)\textsuperscript{18}. They have described a new modification of the selective N-alkylation reaction of secondary amines with alkyl halides in the presence of excess potassium hydride and triethylamine (10 equiv.) to give the corresponding tertiary amines in satisfactory yields. Triethylamine appeared to be a critical factor and it was presumed to act as a scavenger of excess alkyl halide. This is a useful
method but the use of metal hydrides would present a problem particularly if either the secondary amine or alkyl halide contains acidic functional groups.

![Scheme 2.8](image)

Chiappe et al. (2003)\textsuperscript{19}: A simple method for the synthesis of secondary amines selectively using ionic liquids as solvent had recently been reported. Secondary amines are formed by a nucleophilic substitution reaction between primary amines and alkyl tosylates or alkyl halides. Ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF\textsubscript{6}], have ultra-low volatility and therefore provide an advantage over volatile organic solvents.

![Scheme 2.9](image)

Moore et al. (2005)\textsuperscript{20}: One of the most frequently used procedures in the synthesis of tertiary amines is the N-alkylation of primary and secondary amines with alkyl halides in the presence of base. Hüning's base has been reported to be a suitable base for the direct formation of tertiary amines via N-alkylation of secondary amines by alkyl halides in acetonitrile. However, the use of excess base (1.5 equiv.) in the reaction makes it unsuitable for base-sensitive functional groups and it is also undesirable from an environmental point of view.

![Scheme 2.10](image)
Salvatore et al. (2001)\textsuperscript{21}: The Mitsunobu reaction employs a covalently activated amine derivative used in the synthesis of amines. This reaction is a coupling of a primary or secondary alcohol with a compound containing an acidic proton (e.g. a sulfonamide) and is carried out in the presence of triphenylphosphine and diethylazodicarboxylate (DEAD). An example is depicted in Scheme 2.11. This particular reaction led to the formation of an anti-tumour polyamine after a series of synthetic steps. Thereafter, more versatile Mitsunobu reagents have been developed. However, in general, the Mitsunobu reaction is not often used on large scale due to the thermal hazards associated with azodicarboxylates.

![Scheme 2.11](image)

Glennon et al. (1981)\textsuperscript{22}: The traditional approach to the synthesis of dimethylamines by the N-alkylation of dimethylamine with alkyl halides at high temperatures and pressure was described.

![Scheme 2.12](image)
2.1.3. General Reaction mechanism of N-Alkylation

Amine can react as a nucleophile with alkyl halides via substitution reactions (S₈2). If the N-alkylation was carried out using alkyl halide as an alkylating agent, the mechanism follows two steps.

Step: 1

The amine N functions as the nucleophile and attacks the electrophilic C of the alkyl halide displacing the halide and creating the new C-N bond.

Step: 2

An acid/base reaction, the base (excess amine) deprotonates the positive N (ammonium) centre creating the alkylation product, here a secondary amine.

![Scheme 2.13](image-url)

Recently, metal catalyzed N-alkylation of amine by alcohol was reported in literature.

![Scheme 2.14](image-url)
The N-alkylation of amines is thought to proceed by the dehydrogenation of alcohols to aldehydes via hydrogen transfer from alcohol to Pd-complex, giving aldehyde and Pd-hydride complex. This is followed by the formation of imines from aldehydes and amines and finally the hydrogenation of imines to amines.
CHAPTER 2

Study on Lewis acid catalyzed N-alkylation reactions

Part-2

Iodine-catalyzed N-alkylation of tosylhydrazones with benzylic alcohols
2.2.1. Introduction:

The N-alkylation of tosylhydrazones represents one of the most important C-N bond formation methodologies in organic synthesis. The N-alkylated hydrazones have various applications in organic synthesis as useful synths and hydrazones constitute an important class of biologically active drug molecules which has attracted attention of medicinal chemists due to their wide range of pharmacological properties. These compounds are being synthesized as drugs by many researchers in order to combat diseases with minimal toxicity and maximal effects. A number of hydrazone derivatives have been reported to exert notably antimicrobial, antihypertensive, anticonvulsant, analgesic, anti-inflammatory, antituberculosis, antitumoral, antiproliferative and antimalarial activities. Biological activities of various hydrazones are well reported in literature (Fig. 2.3).

![Diagram of bio-active N-alkylated hydrazones](image)

Figure 2.3: Examples of bio-active N-alkylated hydrazones
Generally, this transformation is carried out using alkyl halides in the presence of stoichiometric amount of base. But, the use of alkyl halides is undesirable from an environmental point of view, and generate wasteful salts as by-products. Cahhi et al. reported the N-alkylation of tosylhydrazones using phase transfer catalyst. Among a variety of approaches for the N-alkylation of tosylhydrazones, alcohols are arguably one of the most ideal substrates that are receiving more attention. In principle, C-N bond formation by direct substitution of a hydroxyl group is difficult because of its poor leaving group ability. Therefore, hydroxyl groups usually require pre-activation through transformation into good leaving groups such as halides, carboxylates, and carbonates before the treatment with tosylhyrazones. However, such a process inevitably produces salt waste, which would set limits for the industrial application and for the scope of substrates.

2.2.2. Review of literature

To the best of our knowledge only one report is available in the literature for the N-alkylation of tosylhydrazones.

Raji Reddy et al. (2009): N-Alkylation of tosylhydrazones in the presence of an acid catalyst is described for the first time. Tris(pentafluorophenyl) borane was found to be a mild and efficient catalyst when benzylic alcohols were used as the alkylation agents.

\[
\begin{align*}
\text{Ar} & \text{N} \equiv \text{N} \overset{\text{Ts}}{\text{H}} + \overset{\text{Ar}^1 \text{OH}}{\text{R}} & \overset{\text{B(CF}_5\text{F}_3)_3 (5 \text{ mol\%})}{\text{CH}_2\text{Cl}_2, \text{rt}, 18-24 \text{ h}} & \overset{\text{Ar} \text{N} \equiv \text{N} \overset{\text{Ts}}{\text{Ar}}}{} \\
\text{Ar} &= \text{aryl, } \text{Ar}^1 = \text{aryl, } \text{R} = \text{aryl, alkyl, H}
\end{align*}
\]

Scheme 2.15
2.2.3. Objective:

Despite significant recent advances in the area of C-N bond formation, there remains room for improvement, such as increase of catalyst stability, lowering reaction temperature and increase of yield in the carbon–nitrogen single bond formation between tosyldrazones with an alcohol.

To the best of our knowledge, there are no examples of the iodine-catalyzed N-alkylation of tosyldrazones with alcohols. Therefore, development of a general, efficient and readily available catalyst like molecular iodine for this valuable transformation is highly desirable.

2.2.4. Present work

In recent years, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations due to its moderate Lewis acidity and water tolerance.\textsuperscript{36-42} Molecular iodine has been used to be a versatile catalyst for alkylation of 1,3-dicarbonyl compounds and 4-hydroxycoumarines,\textsuperscript{43,44} synthesis of bis(indolyl)methane,\textsuperscript{45} Michael addition of indole and pyrrole to nitroolefins\textsuperscript{46} etc. More recently, iodine-catalyzed transformation of molecules containing oxygen functional groups have been reported in literature.\textsuperscript{47} Herein we describe a highly efficient method for the C-N bond formation via molecular iodine–catalyzed N-alkylation reaction of tosyldrazones with benzylic as well as benzhydric alcohols.

Scheme 2.16: Molecular iodine catalyzed N-alkylation of tosyldrazones
2.2.5. Results and discussion

Initially, we attempted the N-alkylation of N-benzylidene-4-methylbenzene sulfonohydrazide (1a) with 1-phenylethanol (2a) in dichloromethane using 20 mol % of iodine as catalyst and it was observed that the reaction went to completion at room temperature within 20 h to give product 3a in 93% yield (Scheme 2.16).

To obtain the optimized reaction conditions, we have chosen the reaction of N-benzylidene-4-methyl benzene sulfonohyrazide with 1-phenylethanol in the presence of molecular iodine as Lewis acid catalyst. First we examined the solvent suitability for this reaction and the results are summarized in Table 2.1. The reaction in DMSO did not proceed well and in THF afforded only 10% of the product with several unwanted side products. After substantial experimentation with different solvents (C₂H₄Cl₂, 80 % yield; CH₃CN, 55% yield; CH₃NO₂, 60% yield), dichloromethane (92% yield), came out as a solvent of choice. With this encouraging result, next we investigated the amount of iodine required to catalyze the transformation. To start with, we have used 10 mol% of iodine which afforded the products in 45% yield, after 20 h. Use of 15 mol% of iodine improved the yield to 75% with the reaction time almost same as that of 10 mol%. On other hand, using 20 mol% of iodine as catalyst the product yield was increased to 94% in 20 h and 20 mol% of iodine has been used as catalyst for further reactions.

To check the versatility of iodine catalyzed N-alkylation reaction, we next investigated the reaction of tosylhydrazones of different aldehydes with a series of
substituted benzylic alcohols under the optimized conditions. The results are summarized in Table 2.2.

Table 2.1. Optimizing the reaction conditions for the N-alkylation of tosylhydrazone (1a) with 1-phenylethanol (2a) using iodine as catalyst.\textsuperscript{a}

\[
\begin{array}{cccc}
\text{Entry} & \text{Solvent} & T \, [\degree C] & \text{Time} \, [\text{h}] & \text{Yield} \, [%] \text{b} \\
1 & \text{DMSO} & 25 & 25 & - \\
2 & \text{THF} & 25 & 25 & 10 \\
3 & \text{C}_2\text{H}_4\text{Cl}_2 & 25 & 20 & 80 \\
4 & \text{CH}_3\text{CN} & 25 & 20 & 55 \\
5 & \text{CH}_2\text{Cl}_2 & 25 & 20 & 92 \\
6 & \text{CH}_3\text{NO}_2 & 25 & 25 & 60 \\
\end{array}
\]

\textsuperscript{a}All reactions were performed with tosylhydrazone (1 mmol), 1-phenylethanol (1.2 mmol), and iodine (20 mol %) in the indicated solvent. \textsuperscript{b}Isolated yield after washing with 10% hexane in ethyl acetate.

N-alkylations of N’-benzylidene-4-methylbenzenesulfonohydrazide (1a) with benzylic alcohols (2a-2f) bearing electron–donating and electron-withdrawing groups, proceeded smoothly to give the corresponding N–alkylated products in moderate to good yields (entries 7-12, Table 2.2). Similarly, N’-(4-methylbenzylidene)–4-methylbenzene sulfonohydrazide (1c) and 4–methyl–N’-(4-nitrobenzylidene) benzenesulfonohydrazide (1d) with benzylic alcohols 2a to 2d also undergo N- alkylation with smooth conversion to give the desired products in substantial yields (entries 13-16, Table 2.2).
Table 2.2. Iodine-catalyzed N-alkylations of aldehyde tosylhydrazones using benzylic alcohols.

$$
\text{Ar} \quad N \quad N \quad \text{Ts} \quad + \quad \text{Ar}^1 \quad \text{R} \quad \text{I}_2 \quad (20 \text{ mol } \%) \quad \xrightarrow{\text{CH}_2\text{C}_2 \text{, rt}} \quad \text{Ar} \quad N \quad N \quad \text{Ts}$$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tosylhydrazone</th>
<th>Benzylic alcohol</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>18</td>
<td>3a</td>
<td>92\ Reports</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2b</td>
<td>18</td>
<td>3b</td>
<td>88\ Reports</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2c</td>
<td>20</td>
<td>3c</td>
<td>80\ Reports</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2d</td>
<td>18</td>
<td>3d</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2e</td>
<td>20</td>
<td>3e</td>
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<td>1a</td>
<td>2f</td>
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<td>3f</td>
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78
<p>| | | | | |</p>
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<thead>
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<th></th>
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<th></th>
</tr>
</thead>
</table>
| 11 | 1b | 2e | 20 | \[
Ts \begin{array}{c}
N \vDash 2-ClC_6H_4 \\
\text{Ph}
\end{array} \\
\begin{array}{c}
4-\text{MeC}_6\text{H}_4
\end{array}
\]
|   |   |   |   | 65 |
| 12 | 1b | 2f | 18 | \[
Ts \begin{array}{c}
N \vDash 2-ClC_6H_4 \\
\text{Ph}
\end{array} \\
\begin{array}{c}
2-\text{ClC}_6\text{H}_4
\end{array}
\] 52°
| 13 | T\(\begin{array}{c}
N \vDash 3-\text{OMeC}_6\text{H}_4
\end{array}
\) | 1c | 2a | 18 | \[
Ts \begin{array}{c}
N \vDash 3-\text{OMeC}_6\text{H}_4 \\
\text{Ph}
\end{array} \\
\begin{array}{c}
\text{Ph}
\end{array}
\] 75 |
| 14 | 1c | 2b | 20 | \[
Ts \begin{array}{c}
N \vDash 3-\text{OMeC}_6\text{H}_4 \\
\text{4-MeC}_6\text{H}_4
\end{array} \\
\begin{array}{c}
\text{3n}
\end{array}
\] 66°
| 15 | 1c | 2c | 18 | \[
Ts \begin{array}{c}
N \vDash 3-\text{OMeC}_6\text{H}_4 \\
\text{4-ClC}_6\text{H}_4
\end{array} \\
\begin{array}{c}
\text{3o}
\end{array}
\] 55°
| 16 | 1c | 2d | 20 | \[
Ts \begin{array}{c}
N \vDash 3-\text{OMeC}_6\text{H}_4 \\
\text{Ph}
\end{array} \\
\begin{array}{c}
\text{Ph}
\end{array}
\] 63 |
| 17 | T\(\begin{array}{c}
N \vDash 4-\text{NO}_2\text{C}_6\text{H}_4
\end{array}
\) | 1d | 2a | 20 | \[
Ts \begin{array}{c}
N \vDash 4-\text{NO}_2\text{C}_6\text{H}_4 \\
\text{Ph}
\end{array} \\
\begin{array}{c}
\text{3q}
\end{array}
\] 95 |
| 18 | 1d | 2b | 18 | \[
Ts \begin{array}{c}
N \vDash 4-\text{NO}_2\text{C}_6\text{H}_4 \\
\text{4-MeC}_6\text{H}_4
\end{array} \\
\begin{array}{c}
\text{3r}
\end{array}
\] 90°
| 19 | 1d | 2c | 18 | \[
Ts \begin{array}{c}
N \vDash 4-\text{NO}_2\text{C}_6\text{H}_4 \\
\text{4-ClC}_6\text{H}_4
\end{array} \\
\begin{array}{c}
\text{3s}
\end{array}
\] 83°
| 20 | 1d | 2d | 20 | \[
Ts \begin{array}{c}
N \vDash 4-\text{NO}_2\text{C}_6\text{H}_4 \\
\text{Ph}
\end{array} \\
\begin{array}{c}
\text{Ph}
\end{array}
\] 78°

\*All reactions were performed with tosylhydrazones (1 mmol), benzylic alcohols (1.2 mmol), and iodine (20 mol %) in dichloromethane. \*Isolated yield after washing with 10% hexane in ethyl acetate.
\*Novel compounds
Next, the reaction was extended to simple primary alcohols such as benzyl alcohols as the substrates for N-alkylation of tosylhydrazones under the same reaction conditions, where, disappointingly, the corresponding N-alkylated products were obtained in low yields (10-15%).

2.2.6. Plausible mechanism:

Although the exact mechanism is not known at this stage, can only be speculated (Fig.2.4) based on the experimental observations. We have previously observed that with a catalytic amount of iodine, benzylic alcohols were rapidly converted to dimeric ether (A) by the elimination of water. Presumably, in the presence of a nucleophile, the ether is polarized by iodine and generates more stable benzylic carbocation (B). The formation of benzylic carbocation is well-documented and has been reported in the literature. The nucleophilic attack of tosylhydrazone moiety on to the resulting benzylic carbocation generated the desired product. Support for this mechanism was obtained from the isolation of the symmetric ether at the initial stages (within 1-2 h) whose structure was confirmed by NMR and which after appropriate time (mentioned in Table 2.1) was fully converted to the corresponding N-alkylated products.

![Figure 2.4: Plausible mechanism for the iodine catalyzed N-alkylation](image)

80
This concluded that iodine act as mild Lewis acid and more efficient for this reaction. When the reaction was carried out in presence of 20 mol% of iodine at room temperature for 4 to 6 h, it has been observed that the ether A was the major product and only with the increase in the mol% of iodine, the desired product was formed. Further, it was observed that the ether was completely converted to the desired product when the reaction was stirred at room temperature for 18 to 20 h.

2.2.7. Conclusion

In summary, we have successfully employed molecular iodine as an efficient catalyst to promote N-alkylation of tosylhydrazones using secondary benzylic alcohols, affording the N-alkylated tosylhydrazone derivatives in good to excellent yields. The notable advantages of this method are broad scope, mild reaction conditions, operational simplicity, direct use of alcohols and the use of inexpensive and non-toxic catalyst. This method is energy saving, environmentally friendly since water is the only side product. In addition, due to the easy availability of the starting materials and catalyst, this reaction may prove to be very useful in organic synthesis. Further studies in this area to explore the mechanism and synthetic applications of this reaction are being carried out in our laboratory.

2.2.8. Experimental Section

General experimental procedure for iodine-catalyzed N-alkylation of aldehyde tosylhydrazones using benzylic alcohols:

To a stirred solution of benzylic alcohol (1 mmol) in dichloromethane (5 ml), were added tosylhydrazone (1.2 mmol) and 20 mol% iodine. The reaction mixture was stirred at room temperature for appropriate time mentioned in Table 2.2 and the reaction was monitored by TLC. After the completion of the reaction, the mixture
was quenched with 10% solution of sodium thiosulfite and separated organic layer was washed with water, brine and then concentrated. The crude solid was washed with 10% hexane in ethyl acetate to give the corresponding N-alkylated products.

2.2.9. Characterization of the products

Compounds 3d and 3p were previously reported and their structures were confirmed by comparison of their spectroscopic data with the reported data. Characterization data for some new compounds are given below.

Compound (3a): Pale yellow solid. m.p.: 125–128 °C. IR (neat): ν = 3021, 2938, 1593, 1167 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.13 (s, 1H, =CH–), 7.68–7.76 (dd, 2H, ArH), 7.59–7.57 (dd, J = 9.6 Hz, 2H, ArH), 7.35–7.40 (m, 5 H, ArH), 7.22–7.30 (m, 5H, ArH) 5.67–5.72 (q, J = 7.2 Hz, 1H, CH), 2.40 (s, 3H, Ar–CH₃), 1.48–1.49 (d, J = 6.8 Hz, 3H, –CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 153.83, 143.86, 140.83, 135.77, 134.31, 130.49, 129.47, 128.65, 128.50, 128.12, 127.64, 127.40, 127.11, 58.70, 21.58, 16.92 ppm. LC-MS: m/z calcd for C₂₂H₂₂N₂O₂S 378.14; found 379.2 (M⁺).

Compound (3b): Pale yellow oil. IR (neat): ν = 3024, 2945, 1596, 1339, 1162 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.11 (s, 1H, =CH–), 7.69–7.71 (dd, J = 8.4 Hz, 2H, ArH), 7.57–7.59 (dd, J = 9.2 Hz, 2H, ArH), 7.34–7.40 (m, 5 H, ArH), 7.21–7.28 (m, 2H, ArH), 7.03–7.14 (m, 2H, ArH) 5.64–5. (q, J = 6.8 Hz, 1H, CH), 2.41 (s, 3H, Ar–CH₃), 2.32 (s, 3H, Ar–CH₃), 1.45–1.47 (d, J = 7.2 Hz, 3H, –CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 153.60, 143.77, 137.77, 137.05, 135.87, 134.36, 130.41, 129.42, 129.15, 128.61, 128.11, 127.61, 126.99, 58.44, 21.57, 21.03, 16.77 ppm. LC-MS: m/z calcd for C₂₃H₂₄N₂O₂S 392.16; found 392.9 (M⁺).
Compound (3c): Light brown solid. m.p.: 110–113 °C. IR (neat): ν = 3060, 2919, 1686, 1588, 1338, 1162 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.25 (s, 1H, =CH–), 7.60–7.62 (m, 4H, ArH), 7.37–7.42 (m, 3H, ArH), 7.30–7.32 (m, 2H, ArH), 7.21–7.27 (m, 4H, ArH), 5.54–5.59 (q, J = 7.2Hz, 1H, CH), 2.41 (s, 3H, Ar–CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 1156.15, 144.01, 139.38, 135.55, 134.06, 133.28, 130.83, 129.45, 128.73, 128.70, 128.49, 128.01, 127.82, 58.45, 21.56, 17.56 ppm. LC-MS: m/z cclcd for C₂₂H₂₂N₂O₂S 412.9; found 413.2 (M⁺).

Compound (3e): Pale yellow solid. m.p.: 118–121 °C. IR (neat): ν = 3021, 2940, 1591, 1339 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.14 (s, 1H, =CH–), 7.50–7.52 (dd, J = 8.4 Hz, 2H, ArH), 7.41–7.44 (m, 2H, ArH), 7.21–7.32 (m, 7H, ArH), 7.14–7.16 (dd, J = 8.0 Hz, 2H, ArH) 7.08–7.10 (dd, J = 8.0 Hz, 2H, ArH), 7.02–7.04 (dd, J = 8.0 Hz, 2H, ArH), 6.86 (s, 1H, CH), 2.35 (s, 3H, Ar–CH₃), 2.30 (s, 3H, Ar–CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 151.38, 143.70, 138.40, 137.18, 135.50, 135.15, 134.47, 130.14, 129.15, 129.09, 129.04, 128.90, 128.55, 128.19, 127.43, 127.37, 66.74, 21.52, 21.06 ppm. LC-MS: m/z cclcd for C₂₈H₂₆N₂O₂S 454.0; found 455.2 (M⁺).

Compound (3f): Pale yellow oil. IR (neat): ν = 3025, 2939, 1598, 1337, 1162 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.24 (s, 1H, =CH–), 7.44–7.51 (m, 5H, ArH), 7.31–7.36 (m, 4H, ArH), 7.17–7.25 (m, 6H, ArH), 7.05–7.12 (m, 4H, ArH), 2.36 (s, 3H, Ar–CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 152.11, 143.89, 137.63, 136.52, 135.34, 133.98, 131.27, 130.37, 129.51, 129.20, 129.04, 128.84, 128.64, 128.29, 128.09, 127.56, 126.51, 64.44, 21.54 ppm. LC-MS: m/z cclcd for C₂₇H₂₃ClN₂O₂S 474.12; found 475.2 (M⁺).

Compound (3g): White solid. m.p.: 133–136 °C. IR (neat): ν = 3059, 2982, 1597, 1350, 1166 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.26 (s, 1H, =CH–), 7.84–7.86
(dd, J = 9.2 Hz, 1H, ArH), 7.78–7.80 (dd, J = 8.0 Hz, 2H, ArH), 7.42–7.44 (d, J = 7.6 Hz, 2H, ArH), 7.22–7.35 (m, 8H, ArH), 5.92–5.94 (q, J = 7.2 Hz, 1H, CH), 2.40 (s, 3H, Ar–CH₃), 1.60–1.62 (d, J = 6.8 Hz, 3H, –CH₃) ppm. \(^{13}\)C NMR (100 MHz, CDCl₃): 144.12, 143.86, 140.08, 135.69, 134.28, 132.10, 129.65, 129.59, 128.72, 128.22, 127.51, 126.90, 126.78, 57.80, 21.60, 16.13 ppm. LC-MS: m/z calcd for C₂₂H₂₁ClN₂O₂S 412.10; found 413.2 (M⁺).

Compound (3h): White solid. m.p.: 140–143 °C. IR (neat): ν = 3061, 2982, 1596, 1380, 1165 cm⁻¹. \(^{1}\)H NMR (400 MHz, CDCl₃): δ = 8.25 (s, 1H, –CH–), 7.83–7.85 (dd, J = 9.6Hz, 1H, ArH), 7.78–7.80 (d, J = 8.4 Hz, 2H, ArH), 7.21–7.31 (m, 7H, ArH), 7.12–7.14 (d, J = 8.0 Hz, 2H, ArH), 5.86–5.91(q, J = 7.2 Hz, 1H, CH), 2.41 (s, 3H, Ar–CH₃), 2.32 (s, 3H, Ar–CH₃), 1.55–1.59 (d, J = 12.8 Hz, 3H, –CH₃) ppm. \(^{13}\)C NMR (100 MHz, CDCl₃): 144.05, 143.74, 137.17, 136.99, 135.80, 134.26, 132.16, 130.61, 129.63, 129.56, 129.36, 128.35, 128.20, 126.88, 126.80, 126.71, 57.61, 21.60, 21.04, 16.03 ppm. LC-MS: m/z calcd for C₂₃H₂₃ClN₂O₂S 426.10; found 427.2 (M⁺).

Compound (3i): Off white solid. m.p.: 121–123 °C. IR (neat): ν = 3024, 2945, 1596, 1339, 1162 cm⁻¹. \(^{1}\)H NMR (400 MHz, CDCl₃): δ = 8.34 (s, 1H, –CH–), 7.82–7.84 (dd, J = 9.6 Hz, 1H, ArH), 7.73–7.75 (d, J = 8.4 Hz, 2H, ArH), 7.31–7.33 (m, 7H, ArH), 7.25–7.29 (m, 2H, ArH), 5.79–5.84 (q, J = 7.2 Hz, 1H, CH), 2.42 (s, 3H, Ar–CH₃), 1.55–1.57 (d, J = 8.8 Hz, 3H, –CH₃) ppm. \(^{13}\)C NMR (100 MHz, CDCl₃): 144.33, 144.31, 138.81, 135.48, 134.43, 133.41, 131.90, 130.94, 129.76, 129.63, 128.77, 128.34, 128.13, 126.96, 126.84, 57.55, 21.60, 16.69 ppm. LC-MS: m/z calcd for C₂₂H₂₀Cl₂N₂O₂S 446.06; found 447.2 (M⁺), 449.0 (M+2).
Compound (3j): Brown solid. m.p.: 137–139 °C. IR (neat): ν = 3060, 2941, 1686, 1588, 1332, 1161 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.39 (s, 1H, =CH–), 7.61–7.64 (m, 3H, ArH), 7.73–7.75 (d, J = 8.4 Hz, 2H, ArH), 7.21–7.32 (m, 9H, ArH), 7.15–7.19 (m, 5H, ArH), 7.11 (s, 1H, CH), 2.38 (s, 3H, Ar–CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 144.16, 142.89, 137.89, 135.25, 134.20, 130.52, 130.08, 129.61, 129.37, 128.96, 128.40, 127.63, 127.44, 127.28, 126.85, 126.75, 66.46, 21.57 ppm. LC-MS: m/z cacld for C₂₇H₂₃ClN₂O₂S 474.12; found 447.2 (M+2), 475.2 (M+).

Compound (3k): Pale yellow solid. m.p.: 111–113 °C. IR (neat): ν = 3032, 2944, 1682, 1581, 1336, 1165 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.36 (s, 1H, =CH–), 7.63–7.66 (m, 3H, ArH), 7.26–7.28 (m, 4H, ArH), 7.19–7.24 (m, 8H, ArH), 7.09–7.18 (m, 3H, ArH) 2.38 (s, 3H, Ar-CH₃), 2.33 (s, 3H, Ar–CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 144.09, 142.73, 138.00, 137.35, 135.38, 134.75, 134.18, 132.19, 130.45, 129.59, 129.34, 129.07, 128.94, 128.85, 128.37, 127.52, 126.82, 126.76, 66.21, 21.57, 21.09 ppm. LC-MS: m/z cacld for C₂₈H₂₅ClN₂O₂S 488.13; found 489.2 (M⁺).

Compound (3l): Pale yellow oil. IR (neat): ν = 3026, 2939, 1598, 1337, 1162 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.37 (s, 1H, =CH–), 7.66–7.68 (m, 3H, ArH), 7.27–7.29 (m, 4H, ArH), 7.22–7.25 (m, 8H, ArH), 7.09–7.20 (m, 3H, ArH) 2.38 (s, 3H, Ar-CH₃), 2.33 (s, 3H, Ar–CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 144.11, 142.83, 138.03, 137.35, 135.58, 134.85, 134.20, 132.21, 130.46, 129.55, 129.35, 129.08, 128.95, 128.86, 128.39, 127.55, 126.89, 126.78, 66.23, 21.59, 21.09 ppm. LC-MS: m/z cacld for C₂₉H₂₃Cl₂N₂O₂S 508.13; found 509.2 (M⁺).

Compound (3n): Brown oil. IR (neat): ν = 3025, 2937, 1596, 1333, 1169 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.08 (s, 1H, =CH–), 7.67–7.71 (m, 2H, ArH),
7.35–7.38 (m, 2H, ArH), 7.18–7.29 (m, 5H, ArH), 7.08–7.14 (m, 2H, ArH), 6.90–6.93 (m, 1H, ArH), 5.68–5.70 (q, J = 7.2 Hz, 1H, CH), 5.29 (s, 3H, -CH3), 3.81 (s, 3H, Ar-OCH3), 2.39 (s, 3H, Ar-CH3) 1.47–149(s, J = 7.2 Hz, 3H, CH3) ppm. 13C NMR (100 MHz, CDCl3): 159.79, 152.79, 143.94, 140.75, 135.73, 129.66, 129.48, 129.31, 128.61, 128.53, 128.43, 128.14, 127.68, 127.57, 127.43, 127.07, 120.63, 116.71, 116.58, 116.45, 111.93, 58.62, 55.30, 53.47, 21.58, 16.89 ppm. LC-MS: m/z cacld for C23H24N2O3S 408.51; found 409.2 (M+).

Compound (3o): Pale yellow oil. IR (neat): ν = 3032, 2939, 1598, 1337, 1162 cm⁻¹.
1H NMR (400 MHz, CDCl3): δ = 8.18(s, 1H, =CH–), 7.67–7.71 (m, 2H, ArH), 7.60–7.62 (d, J = 8.4 Hz, 1H, ArH), 7.25–7.31 (m, 3H, ArH), 7.13–7.22 (m, 7H, ArH), 6.94–6.96 (m, 1H, ArH), 5.56–5.58 (q, J = 7.2 Hz, 1H, CH), 3.83 (s, 3H, Ar-OCH3), 2.40 (s, 3H, Ar-CH3) 1.43–145 (s, J = 6.8 Hz, 3H, CH3) ppm. 13C NMR (100 MHz, CDCl3): 159.83, 155.14, 144.07, 139.34, 135.55, 135.47, 133.29, 129.75, 129.47, 128.82, 128.67, 128.52, 128.02, 120.78, 116.69, 112.22, 58.39, 55.33, 21.57, 17.52 ppm. LC-MS: m/z cacld for C23H23ClN2O3S 442.9; found 443.2 (M+).

Compound (3r): Yellow oil. IR (neat): ν = 3032, 2946, 1594, 1335, 1160 cm⁻¹. 1H NMR (400 MHz, CDCl3): δ = 8.38–8.40 (dd, J = 8.4 Hz 2H, ArH), 7.89 (s, 1H, =CH–), 7.76–7.78 (dd, J = 8.0 Hz, 2H, ArH), 7.60–7.62 (dd, J = 8.8Hz, 2H, ArH), 7.25–7.31 (m, 4H, ArH), 7.11–7.17 (m, 2H, ArH), 5.87–5.93 (q, J = 7.2 Hz, 1H, CH), 2.43 (s, 3H, Ar-CH3), 2.33 (s, 3H, Ar-CH3), 1.59–1.61 (d, J = 7.2 Hz, 3H, –CH3) ppm. 13C NMR (100 MHz, CDCl3): 148.15, 144.50, 143.16, 140.63, 137.45, 136.71, 135.60, 130.49, 129.49, 128.02, 127.46, 126.56, 125.35, 124.31, 123.90, 58.03, 21.62, 21.04, 16.59 ppm. LC-MS: m/z cacld for C23H23N2O4S 437.51; found 438.2 (M+).
Compound (3S): Yellow oil. IR (neat): ν = 3026, 2939, 1597, 1336, 1160 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.18–8.21 (dd, J = 8.8 Hz, 2H, ArH), 8.03 (s, 1H, =CH–), 7.66–7.72 (dd, J = 8.4 Hz, 2H, ArH), 7.64–7.66 (dd, J = 8.0 Hz, 2H, ArH), 7.26–7.33 (m, 7H, ArH), 5.81–5.83 (q, J = 7.2 Hz, 1H, CH), 2.43 (s, 3H, Ar–CH₃), 1.58–1.60 (d, J = 7.2 Hz, 3H, –CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 148.37, 144.92, 144.76, 140.32, 138.59, 135.33, 133.64, 129.83, 128.89, 128.60, 127.91, 127.62, 126.80, 123.98, 69.75, 58.03, 25.30, 21.62, 17.26 ppm. LC-MS: m/z cacl₃ for C₂₂H₂₀ClN₃O₄S 457.9; found 458.0 (M⁺), 459.2 (M+2).

Compound (3t): Yellow oil. IR (neat): ν = 3032, 2938, 1597, 1334, 1164 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.12–8.36 (dd, J = 8.4 Hz 2H, ArH), 8.0 (s, 1H, =CH–), 7.62–7.68 (dd, J = 8.0 Hz, 2H, ArH), 7.45–7.49 (dd, J = 8.4 Hz, 2H, ArH), 7.22–7.40 (m, 10H, ArH), 7.14–7.20 (m, 2H, ArH), 7.10 (s,1H CH), 2.38 (s, 3H, Ar–CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 148.08, 144.63142.39, 142.23, 140.64, 137.69, 135.11, 133.19, 130.00, 129.60, 129.28, 129.06, 128.84, 128.68, 128.39, 127.86, 127.44, 127.39, 127.28, 127.07, 126.56, 126.45, 123.90, 80.03, 66.83, 21.61 ppm. LC-MS: m/z cacl₃ for C₂₂H₂₅N₃O₄S 485.14; found 486.2 (M⁺).
2.2.9.1. Spectra

$^1$H NMR (400 MHz, CDCl$_3$) of compound 3a

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3a
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3b

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3b
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3c

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3c
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3e

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3e
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3f

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3f
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3g

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3g
\[^{1}\text{H NMR (400 MHz, CDCl}_3\text{) of compound 3h}\]

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{) of compound 3h}\]
$^1$H NMR (400 MHz, CDCl₃) of compound 3i

$^{13}$C NMR (100 MHz, CDCl₃) of compound 3i
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3j

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3j
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3k

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3k
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3l

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3l
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3n

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3n
$^1$H NMR (400 MHz, CDCl$_3$) of compound 3o

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 3o
3.3. References