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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Syed Aziz Imam Quadri, Tonmoy C. Das, Shivaji Jadhav & Mazahar Farooqui (2018): Efficient synthesis of tertiary amine by direct N-alkylation of secondary amine with carboxylic acid using Ni (0) encat catalyst, Synthetic Communications, DOI: 10.1080/00397911.2017.1396613

To link to this article: https://doi.org/10.1080/00397911.2017.1396613

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https://doi.org/10.1080/00397911.2017.1396613

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Efficient synthesis of tertiary amine by direct *N*-alkylation of secondary amine with carboxylic acid using Ni (0) encat catalyst

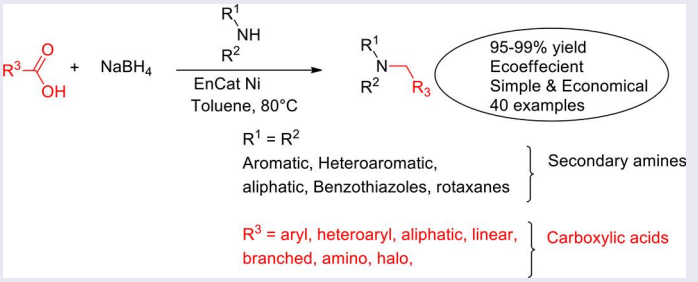
Syed Aziz Imam Quadri, Tonmoy C. Das, Shivaji Jadhav, and Mazahar Farooqui

Department of Chemistry, Dr. Rafiq Zakaria College for Women, Aurangabad, India

ABSTRACT

In this article, direct *N*-alkylation of secondary amines with carboxylic acid is described. Readily available diversified carboxylic acid has been explored on variant secondary amines using encapsulated Nickel as catalyst and inexpensive sodium borohydride as the hydride source. High yields, mild reaction conditions, tolerance to sensitive functional group and facile operational procedure are the significance of the present methodology.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 6 August 2017

KEYWORDS
Encapsulated Ni; *N*-alkylation; sodium borohydride; tertiary amine

Introduction

Tertiary amines are structural motifs in a wide range of biologically active alkaloids, fine chemicals, agrochemicals,[1] and pharmaceuticals.[2] Drugs with amine functionality are designed to mimic or interfere with the action of natural neurotransmitters with amine functionality, such as antihistamine (chlorpheniramines), tricylic antidepressants (amitriptyline, imipramine, loferamine, clomipramine),[3] and antiparkisons drugs (ropinerol and rotigotines).[4] Due to their wide scope in different areas of chemistry and biology, several methodologies for synthesis of tertiary amines have been developed. In generall tertiary amines are synthesized via amide reduction involving two steps; in the first step amide is synthesized followed by the reduction of the amide group with a homogeneous and heterogeneous catalyst in the presence of a hydride source.[5–8] The additional step is a limitation of this methodology, which is not favorable with regard to

CONTACT Mazahar Farooqui mazahar_64@rediffmail.com Department of Chemistry, Dr. Rafiq Zakaria College for Women, Aurangabad, Maharashtra 431001, India.
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Supplemental data for this article can be accessed on the publisher's website.

eco-efficiency and competitiveness. The direct alkylations of secondary amines with alkyl halides or alcohols for the synthesis of tertiary amines are also reported.[9] However lower yield, longer reaction time and requirement of microwave conditions are some of the draw backs of these methods. Although some significance improvements have been made in the direct reductive amination of carbonyl groups, i.e., aldehydes and ketones, the iminium ion/enamide formation with secondary amine is challenging. Different silanes viz., Cl_3SiH/DMF, Et_3SiH/CF_3COOH, and polymethylhydrosiloxane (PMHS)/Ti(OiPr), Et_3SiH/iradium catalyst[11,12] have been used in the catalyst system for the reductive alkylation of secondary amine with aldehydes. However, the required aldehydes are expensive, sparsely available, and unstable. The alkylation of secondary amines with carboxylic acids and sodium borohydride is an efficient method to access tertiary amines and different reports are available in literature with varying degree of success.[13] However there is lot of scope of widening the methodology on diversified and sterically hindered secondary amines with improved reaction conditions. Here we report a simple protocol using encapsulated Nickel as catalyst in the presence of sodium borohydride as hydride source for the synthesis of diverse tertiary amines. Different carboxylic acids are reduced to aldehydes at lower temperature facilitating direct alkylation of varied secondary amines to provide structurally diverse tertiary amines and the results are compared with previous methodology.

Results and discussion

Initially, the feasibility of the approach was demonstrated in the synthesis of *N,N*-dipropylaniline by heating propionic acid and *N*-propylaniline in the presence of sodium borohydride at 50 °C (Fig. 1). A formation of 45% of *N,N*-dipropylaniline (analyzed by HPLC) was observed along with unreacted *N*-propylamine. During the course of the study, few observations were made which helped in predicting the path way of the reaction, thereby providing insights in the optimization and identification of suitable parameters to establish efficient reaction conditions. First observation was the continuous liberation of hydrogen gas which generally results from the proton of carboxylic acid and hydride of sodium borohydride during the reaction. Second, the formation of propionaldehyde along with propan-1-ol was identified during GC analysis. Finally, the formation of sodium tri(propionyloxy) borohydride complex was determined by mass spectral analysis (HRMS) of the reaction mixture. This study led to optimize proper stoichiometric ratio of propionic acid and sodiumborohydride as well as to determine optimum reaction temperature to control the over reduction. Table 1 summarizes the results obtained on using different equivalent of propionic acid and sodium borohydride with varying temperature for the reaction.

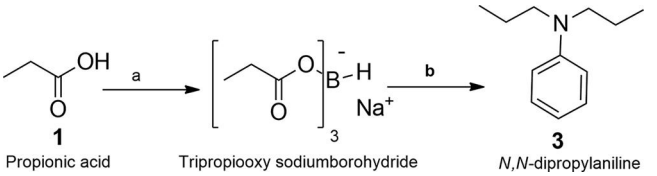


Figure 1. (a) Sodium borohydride, 0 °C, toluene, (b) *N*-propylaniline (**2**), 25–80 °C.

Table 1. Optimization studies in the synthesis of *N, N*–dipropylaniline.

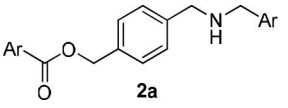
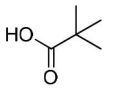
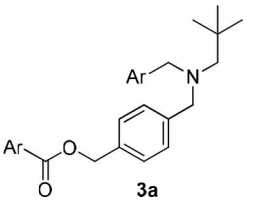
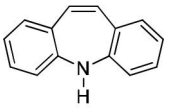
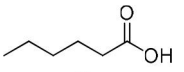
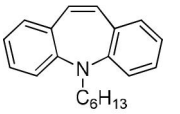
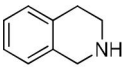
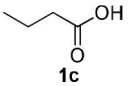
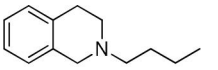
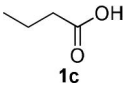
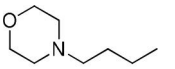
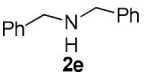
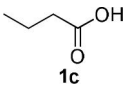
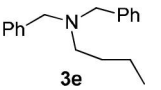
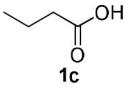
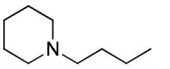
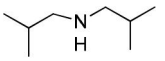
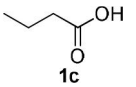
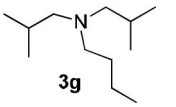
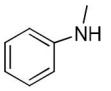
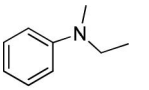
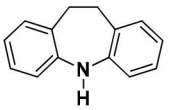
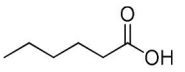
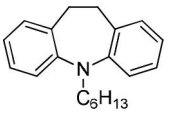
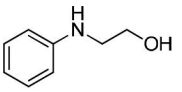
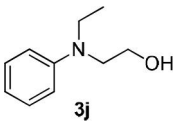
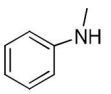
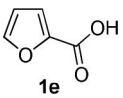
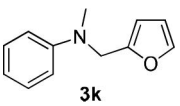
Entry	Equiv. of $NaBH_4$ (mmol)	Equiv. of **1** (mmol)	T_1 (°C)	T_2 (°C)	Compound **3**
1	1	1	80	80	14%
2	1	2	80	80	19%
3	2	3.5	80	80	45%
4	2.5	4	80	80	70%
5	2.5 + 1.5	4	80	80	76%
6	4	4	80	80	64%
7	2.5 + 1.5	4	0	0	0%
8	2.5 + 1.5	4	0	80	80%
9	2.5 + 1.5	4	0	80	99%[P]

T_1 = temperuature before addition secondary amine, T_2 = temperature after addition of secondary amine, P = encapsulated Nickel was added. Toluene used as solvent.

At the outset, 1 equiv each of propionic acid and sodium borohydride were used and only 14% of *N,N*-dipropylaniline was formed. By increasing the quantity of propionic acid, slight increase in the formation of *N,N*-dipropylaniline was observed and 45% *N,N*-dipropylaniline was formed with 3.5 equiv of propionic acid and 2 equiv of sodium borohydride. This initial success helped to further optimize conditions to achieve *N,N*-dipropylaniline with 70% yield using 4 equiv of propionic acid and 2.5 equiv of sodium borohydride. To the same reaction mixture when additional 1.5 equiv of sodium borohydride was added, the yield of *N,N*-dipropylaniline increased to 76%. All the above reactions were performed at 80 °C. Interestingly, the yield of the reaction was decreased (64%) when all of the 4 equiv of sodium borohydride was added at a time. Moreover, when the reaction was performed at 0 to 25 °C with similar mole ratio, no formation of product was observed. Encouraging result was obtained (80% yield) by addition of 2.5 equiv of sodium borohydride to 4 equiv of propionic acid at 0 °C then raising the temperature to 30 °C followed by addition of secondary amine. Subsequently, the temperature increased further to 80 °C followed by addition of 1.5 equiv additional sodium borohydride. The reaction was completed in 8–10 h. To further improve the yield and reduce the reaction time, 2.5% encapsulated Nickel was added along with sodium borohydride. Surprisingly 99% reaction conversion was observed and the reaction time also decreased to 2 h. On increasing the loading of encapsulated Ni to 3%, no significant improvement in reaction time and yield was observed. However, with 1% encapsulated nickel loading, 92% yield was observed with a reaction time of 10 h. To test the efficiency of the catalyst, we recycled the encapsulated Ni catalyst ten times and no significant change in the reactivity was observed. With this optimum reaction conditions in hand, we explored alkylation of varied secondary amines with different carboxylic acids.

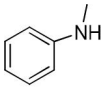
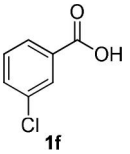
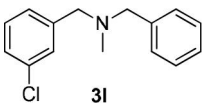
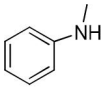
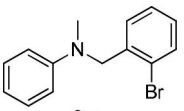
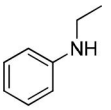
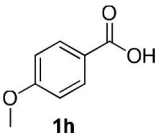
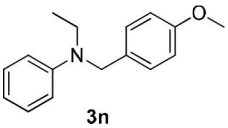
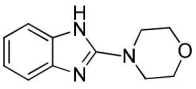
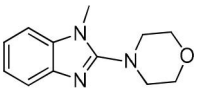
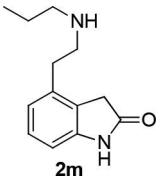
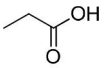
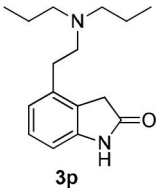
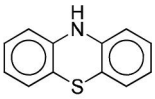
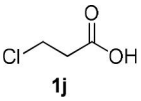
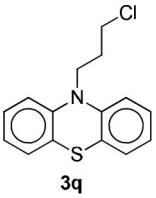
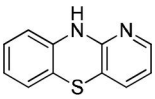
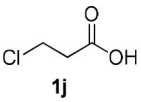
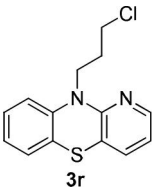
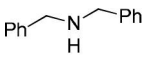
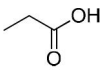
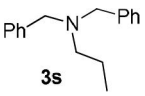
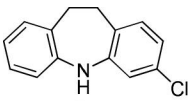
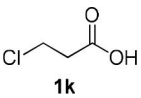
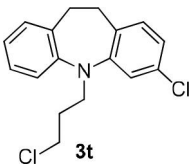
The feasibility and versatility of this novel methodology was demonstrated by investigations on alkylation of a range of substrates with modified variants of both amine substituents as well as carboxylic acid substrates (Table 2). The aliphatic amines **2c** to **2g** on reaction with aliphatic carboxylic acids provided 97–99% yield of corresponding products **3c** to **3g**. The yields of these products were 71 to 90% in previous reported methodologies, thereby highlighting the efficiency of the present method. The present methodology was also explored on simple and steric hindered aromatic amines (**2b** and **2h**) and quantitative yields (99%) were obtained. For the same substrates, the yield was reported to be 82% only in previous methodology. Interestingly in the conversion of **2i** to **3i** using the present method provided 97% yield in 5 h, however the reaction was reported to be not feasible even after 22 h in previous report. Encouraged by the results, we also explored the present methodology on amino benzimidazoles and excellent yields in the range of 95–97% were

Table 2. Synthesis of structurally diverse tertiary amines from corresponding amines and carboxylic acids.

Entry	Substrate-1 secondary amine	Substrate -2 carboxylic acid	Product	Time (h)	Temp. °C	Yield (%)
1	 **2a**	 **1a**	 **3a**	5 48	80 70	98%[p] 25%[f]
2	 **2b**	 **1b**	 **3b**	4 10	80 0	99[p] 82[a]
3	 **2c**	 **1c**	 **3c**	2 8	80 110	98[p] 84[b]
4	 **2d**	 **1c**	 **3d**	2 15	80 110	99[p] 90[b]
5	 **2e**	 **1c**	 **3e**	2 8	80 75	98[p] 82[b]
6	 **2f**	 **1c**	 **3f**	2 8	80 120	99[p] 71[b]
7	 **2g**	 **1c**	 **3g**	2.5 8	70 70	97[p] 88[b]
8	 **2h**	 **1d**	 **3h**	2 18	80 r.t	99[p] 94[c]
9	 **2i**	 **1b**	 **3i**	5 22	80 0	97[p] 0[a]
10	 **2j**	 **1d**	 **3j**	5 18	80 60	98[p] 84[d]
11	 **2h**	 **1e**	 **3k**	4 6	80 70	98[p] 87[e]

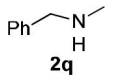
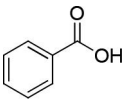
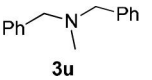
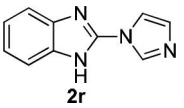
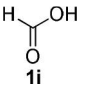
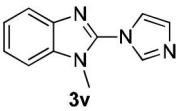
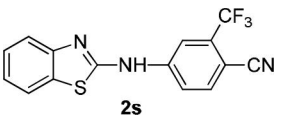
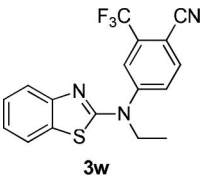
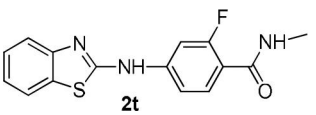
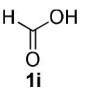
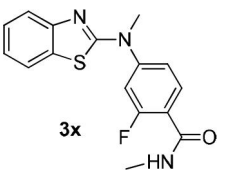
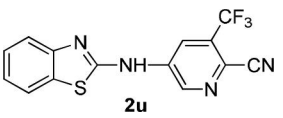
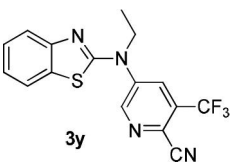
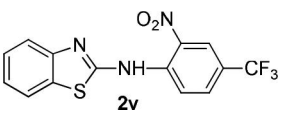
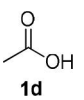
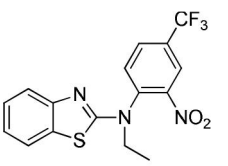
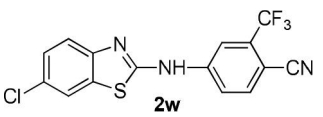
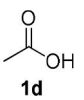
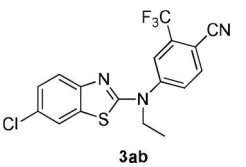
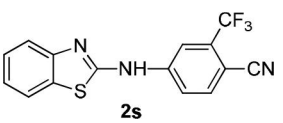
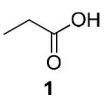
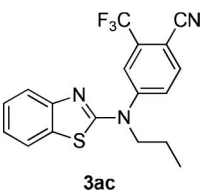
(*Continued*)

Table 2. Continued.

Entry	Substrate-1 secondary amine	Substrate -2 carboxylic acid	Product	Time (h)	Temp. °C	Yield (%)
12	 **2h**	 **1f**	 **3l**	4 6	80 70	97[p] 70[e]
13	 **2h**	 **1g**	 **3m**	4 6	80 70	98[p] 83[e]
14	 **2k**	 **1h**	 **3n**	5 6	80 70	96[p] 83[e]
15	 **2l**	 **1i**	 **3o**	4	75	95
16	 **2m**	 **1**	 **3p**	3	80	98
17	 **2n**	 **1j**	 **3q**	5	80	97
18	 **2o**	 **1j**	 **3r**	6	75	98
19	 **2e**	 **1**	 **3s**	2	80	99
20	 **2p**	 **1k**	 **3t**	7	80	99

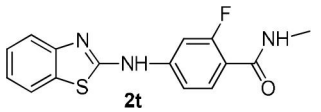
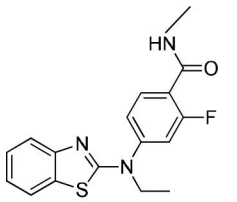
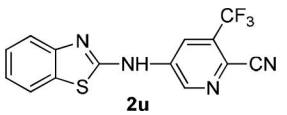
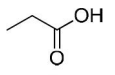
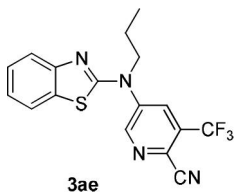
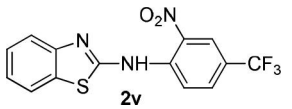
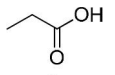
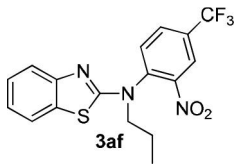
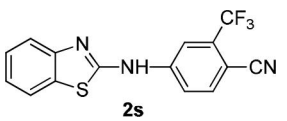
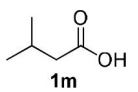
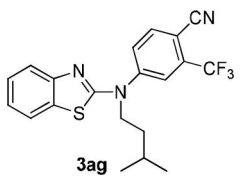
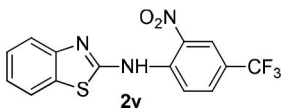
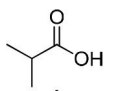
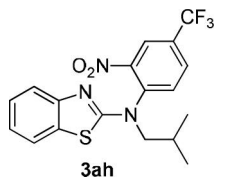
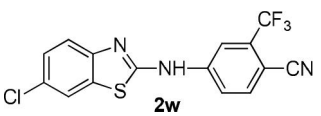
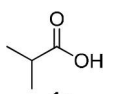
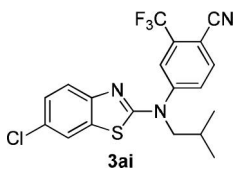
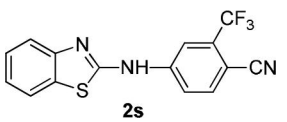
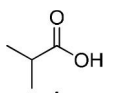
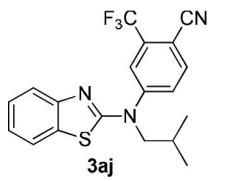
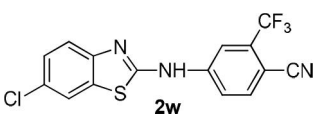
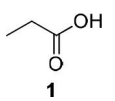
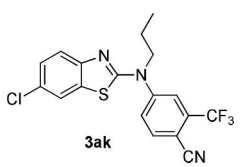
(*Continued*)

Table 2. Continued.

Entry	Substrate-1 secondary amine	Substrate -2 carboxylic acid	Product	Time (h)	Temp. °C	Yield (%)
21	 **2q**	 **1l**	 **3u**	4	80	96
22	 **2r**	 **1i**	 **3v**	3	75	97
23	 **2s**	 **1d**	 **3w**	4	80	96
24	 **2t**	 **1i**	 **3x**	5	75	96
25	 **2u**	 **1d**	 **3y**	6	75	97
26	 **2v**	 **1d**	 **3z**	6	80	95
27	 **2w**	 **1d**	 **3ab**	5	80	97
28	 **2s**	 **1**	 **3ac**	4	80	98

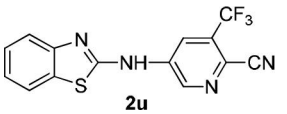
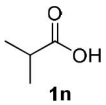
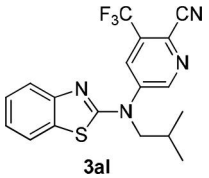
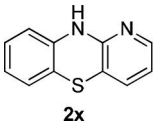
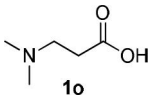
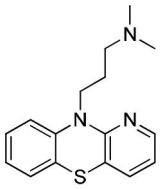
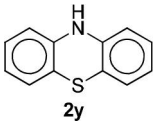
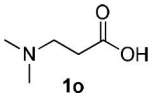
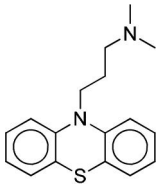
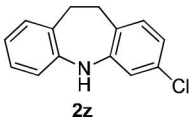
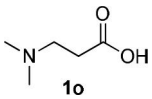
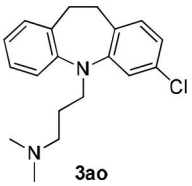
(*Continued*)

Table 2. Continued.

Entry	Substrate-1 secondary amine	Substrate -2 carboxylic acid	Product	Time (h)	Temp. °C	Yield (%)
29	 **2t**	 **1d**	 **3ad**	5	75	97
30	 **2u**	 **1**	 **3ae**	4	75	96
31	 **2v**	 **1**	 **3af**	7	80	97
32	 **2s**	 **1m**	 **3ag**	5	80	96
33	 **2v**	 **1n**	 **3ah**	8	80	97
34	 **2w**	 **1n**	 **3ai**	5	80	98
35	 **2s**	 **1n**	 **3aj**	6	75	96
36	 **2w**	 **1**	 **3ak**	8	75	97

(*Continued*)

Table 2. Continued.

Entry	Substrate-1 secondary amine	Substrate -2 carboxylic acid	Product	Time (h)	Temp. °C	Yield (%)
37	 **2u**	 **1n**	 **3al**	5	80	95
38	 **2x**	 **1o**	 **3am**	6	75	96
39	 **2y**	 **1o**	 **3an**	4	75	97
40	 **2z**	 **1o**	 **3ao**	5	80	98

P=Present work, N = new compound.
[a]Sodium triacetoxyborohydride 3.00 equiv, 3.00 equiv hexanoic acid, DCE.[10]
[b]IrCl(cod) I_2, Et_3SiH, Octane at 120 °C / Toluene at 110 °C.[11a]
[c]Karstedt's catalyst / dppe, $PhSiH_3$.[12a]
[d]CH_3CO_2H (4.5 equiv), $PhSiH_3$ (8 equiv).[12a]
[e]$SnCl_2$. H_2O, PMHS, MeOH, 70 °C.[14]
[f]Pivalaldehyde (10 equiv), acetoxyborohydride (5 equiv), NMP, crown ether, 1 equiv TEA, Ar = 3,5-dimethylphenyl group.[15]

achieved on substrates **2l** and **2r**. In addition, we successfully used the present methodology on carboxylic acid substrates with linear and branched variants (**1a, 1d, 1j, 1i, 1m** and **1n**) on novel amino benzimidazole substrates (**2s** to **2w**) reported recently from our laboratory.[16] High yields (95–97%) were achieved with new compounds **3s** to **3z** and 3**w** to 3**al**. Especially, the alkylation on rotaxane (**2a**) by the steric carboxylic acid **1a** rendered product **3a** in 98% yield in 5 h, almost four time higher that the previous reported method.[15] Finally, we explored our methodology on chlorocarboxylic acid **1a** and amino carboxylic acid **1o**, which on reaction with **2k** to **2z** furnished the known drug substances, imipramine, prothipendyl and promazine(**3am–3ao)** in 96–98% yield.

A plausible mechanism involved in the present methodology is elucidated in Figure 2. Carboxylic acid reacts with sodium borohydride to form acyloxy borohydride complex as determined by HRMS. The hydride ion transfer from boron to carbonyl carbon resulted

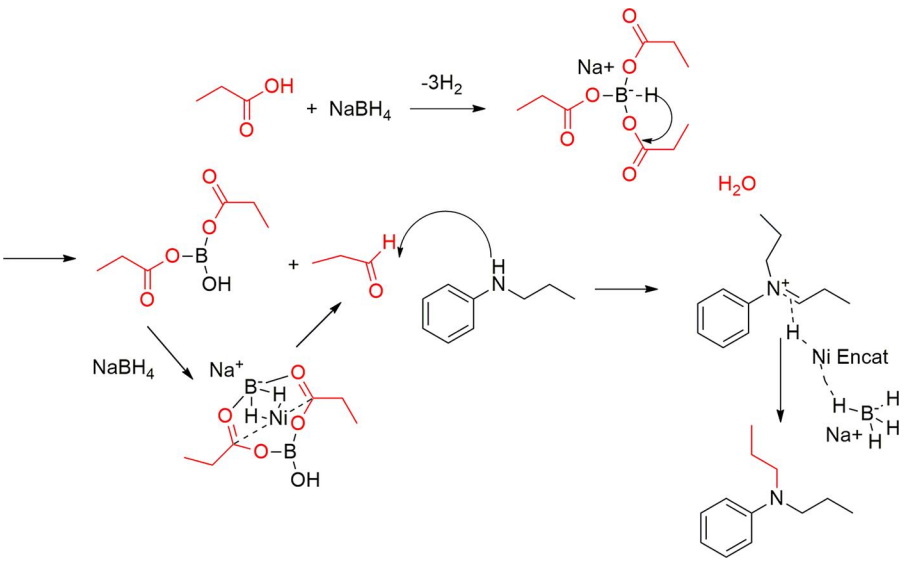


Figure 2. Plausible mechanism for *N*-Propylation.

in the formation of aldehyde, which subsequently reacted with secondary amine to generate tertiary amine via imine formation. Evidence of propionaldehyde formation was determined by GC analysis of reaction mixture and the residue of the product. We presume that encapsulated nickel assists in catalyzing the reduction of imine functionality to amine.

Plausible mechanism

Conclusion

In summary, we report a novel methodology for the direct *N*-alkylation of variant secondary amines with aliphatic, aromatic, heteroaromatic, linear and branched carboxylic acids. Commercially available sodium borohydride and encapsulated Ni were used as catalyst to achieve excellent quantitative yields (95–99%). The versatility of this alkylation method on novel secondary amines, 2-aminobenzothiazoles, was also successfully demonstrated. Previously reported examples were used to compare the effectiveness of this protocol. In comparison, this methodology is mild, eco-efficient and furnishes high yield 95–99%.

Procedure for synthesis of compound (3w): (detailed procedure and spectroscopic data of new compound provided in the supporting information, the products **3a**[15], **3b**[10], **3c**[11a], **3d**[11a], **3e**[11a], **3f**[11a], **3g**[11a], **3h**[12a], **3i**[10], **3j**[12a], **3k**[14], **3l**[14], **3m**[14], **3n**[14], **3o**[16], **3p**[17], **3q**[18], **3s**[19a], **3t**[19b], **3u**[19c], **3v**[16] and **3am**[20a], **3an**[20b], **3ao**[20c] are known compounds and have been reported previously)

To the acetic acid (3.74 g, 6.26 mmol) in toluene (25 mL), sodium borohydride (1.48 g, 3.91 mmol) was added in portions at 0–5 °C. This was followed by addition of 0.125 g EnCat Ni (obtained commercially) to the reaction mixture and gradually the temperature was raised to 25–30 °C. To the resulting mixture compound **2w** (5 g, 1.56 mmol) was added and the temperature was raised to 80 °C, followed by further addition of 0.89 g of sodium borohydride (2.35 mmol) in portions. The progress of the reaction was monitored by TLC. After the completion of reaction, reaction mixture was quenched with 1N HCl to pH 7 to 8

and the separated organic phase was washed with water. Solvent was distilled out under reduce pressure at 50 °C. The product was isolated by crystallization in isopropyl alcohol (30 mL) and conc. hydrochloric acid (1.91 g) followed by filtration and drying to yield 5.76 g hydrochloride salt as white solid, m.p 240 °C–244 °C. IR (cm^{-1})): 3105, 2924, 2231, 1567, 1533, 1460; ^{1}H NMR (400 MHz, DMSO) δ: 0.98 (3H, t, CH_3), 3.05(2H, q, CH_2) 7.26 (1H, t, Ar-CH); 7.4 (1H, t, Ar-CH); 7.72(1H, d, Ar-CH); 7.91(1H, d, Ar-CH); 8.12(1H, d, Ar-CH); 8.21(1H, d, Ar-CH); 8.40(1H, s, Ar-CH). HRMS (ESI) for $C_{17}H_{12}F_3N_3S$ $[M+H]^+$: 348.3102, Anal. Calcd for $C_{17}H_{12}F_3N_3S$: C, 58.78; H, 3.48; N, 12.10 Found: C, 58.75; H, 3.45; N, 12.10.

Acknowledgment

We acknowledge the management of Dr. Rafiq Zakaria College for women Aurangabad.

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