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A Powerful tool for acid catalyzed organic addition and substitution reactions

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A novel green chemistry tool for acid catalyzed reactions has been developed. The multipurpose tool is based on the ability of dry solid materials to donate protons (H^+) to starting materials combined with the simultaneous use of a nucleophile (e.g. NaI). The methods enables the following reactions to be conducted at 20-50°C: selective addition of iodine or alcohols to more substituted carbon in $R_2C=CH_2$ systems (R≠H), esterification reactions, e.g. free fatty acids with methanol, and at higher temperatures, (60-100°C): esterification of free fatty acids with hindered alcohols (isopropanol), addition of iodine to C≡C bonds, opening of oxygen(s) containing heterocyclic rings, selective substitution of primary OH groups to iodine in the presence of other functional groups or secondary alcohol groups, esterification of alcohols with nitriles (R-CN), transesterification of fatty acid triglycerides to biodiesel and selective derivatization of primary hydroxyl group ($-CH_2OH$) over secondary moieties of sugars without any protection. Most of the reactions were performed also by re-used Dowex® cation exchange resin.

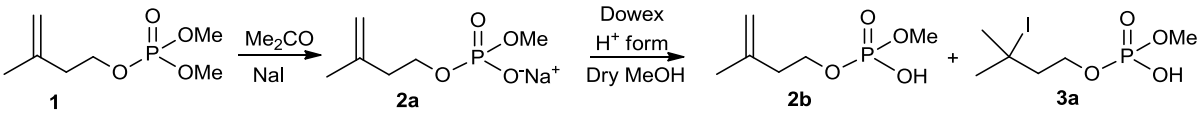
Introduction

Today there is an increasing demand for green chemistry methods and technologies in industrial processes, to reduce waste and to eliminate the use and generation of hazardous substances. Here we describe a novel multipurpose tool to selectively perform organic addition and substitution reactions in solutions based on dry solid materials, which are recyclable, acutely non-toxic and easy to handle. This novel system enables acid-catalyzed organic reactions without involving special reaction conditions or complex separation steps, enabling synthesis of compounds that are difficult or even impossible to prepare by other currently known methods. Typical examples of these reactions include esterification reactions at room temperature with quantitative yields, opening of six membered oxygen-containing heterocyclic rings to produce haloalkanols, selective substitution of the primary HO-group to nucleophiles in the presence of other types of HO-groups and addition of iodine to multiple bonds using alkalimetal iodide (e.g. NaI) as an iodine source.

The tool developed here, is based on the ability of dry solid materials, such as Dowex® resin or solid bisphosphonates, to donate protons (H^+) to starting materials combined with the simultaneous use of a salt form nucleophile (e.g. NaI), which acts either as a catalyst, as in the esterification reactions, or as a reagent, e.g. in the addition of iodine to multiple bonds. Surprisingly, although solid ion exchange resins have been available for a more than a hundred years[1], there are no previous publications in the literature on this specific use. The system developed here resembles in someways those conducted with ionic liquids, e.g. acetylation of alcohols with acetonitrile[2], although isolation of the product is more straightforward in the best case requiring only filtration and solvent evaporation for the product to be ready for the next step.

Results and Discussion

This reaction system was initially discovered by chance when we were trying to develop novel synthesis strategies for prepairing ApppI, the isopentenyl derivative of ATP, which is one of the key metabolic compounds formed when cells are treated with nitrogen containing bisphosphonates.[3] The unexpected reaction was found when attempts were made to prepare the ApppI intermediate **2b** under rather standard conditions as shown in Scheme 1. In this approach, sodium iodide was used as the demethylation agent[4] to prepare compound **2a** from dimethyl derivative **1a** followed by addition of the H^+ form Dowex® resin to exchange the sodium for a proton. Unexpectedly, after solvent evaporation, the residue contained a mixture of two compounds, not only **2b** as expected, but, based on ^1H, ^{13}C, ^{31}P NMR and mass spectrometry data, the second product was verified as compound **3a**. We speculated that the reaction had been made possible due to the presence of trace amounts of NaI among compound **2a** when H^+ Dowex® was added. In the literature, similar selective addition reactions of HI to terminal $H_2C=CR_2$ (R≠H) bonds are extremely rare[5] while addition of iodine to other kinds of double bonds are rather common.



Scheme 1. Discovery of the unexpected reaction.

After a systematic study of this reaction, we noticed that the key to the reaction was the oven-dried solid material containing $-SO_3H$, $-CO_2H$ and/or $-PO_3H_2$ groups as a part of material structure mixed with the dry salt form nucleophile in a protic or polar aprotic solvent. Typically, solid materials containing the above mentioned groups are strong cation exchange resins, such as Dowex® and Amberlyst® type materials, but the addition of HI to terminal $H_2C=CR_2$ (R≠H) bonds was also successful when conducted with solid microporous bisphosphonates[6]. In the case of nucleophiles, sodium iodide was typically used in the reactions to achieve the best yields. In addition, other X^+I_n ($X = K^+, Rb^+, Ni^+, NH_4^+, Mn^{2+}, Sb^{3+}$, n = 1, 2 or 3) salts were tested in the esterification of oleic acid with MeOH, but lower and variable yields were obtained. Addition of bromine to the $H_2C=CR_2$ (R≠H) bond using NaBr as a bromine source was also successful (reactions with bromides using the system reported here are being studied more systemically and will be reported in the near future), but chloride did not react even at elevated temperatures. After realizing that the addition reaction mentioned above was based on a novel reaction strategy to prepare acid catalyzed reactions, we started to systematically map and determine which other transformations would be possible under similar conditions. We have so far tested about 50 different reaction types with the most representative examples of the successful ones compiled in Table 1.

The above described addition reaction was selective for isolated $H_2C=CR_2$ (R≠H) bond systems at room temperature and according to the ^1H NMR spectral data, quantitative conversions could be achieved although isolated yields were lower. It was even possible to prepare monodeuterated compound **5b** when the sodium form of Dowex® resin was treated with DCl/D_2O and the reaction was performed in CD_3OD. Addition reactions of iodine to other types of mono-, di- and trisubstituted double bond systems were tested in preliminary experiments but resulted in either mixtures of products or unreactive starting materials. However, it also seems possible to add iodine to other kinds of double bond systems at elevated temperatures, although this will need to be examined more systematically. In the case of carvone (**6**), it was possible to isolate the iodine adduct **7** after a 2h reaction time at 20°C, but the aromatic carvacrol (**9**) was the main product formed with longer reaction times (>10h). Moreover, in the presence of alcohols as solvents at elevated temperatures (>40°C), ethers **8** were obtained, probably either via direct addition of alcohols to the terminal double bond and/or via substitution of iodide from intermediate **5a**.

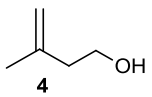
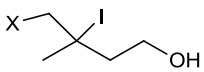
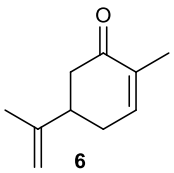
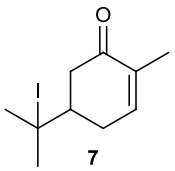
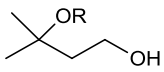
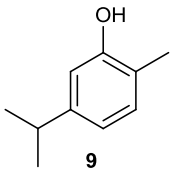
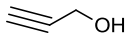
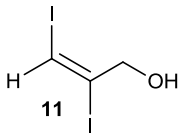
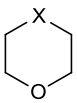
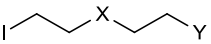
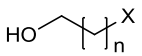
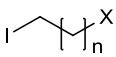
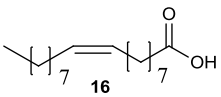
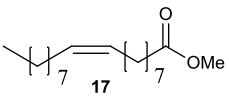
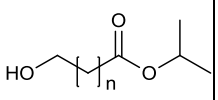
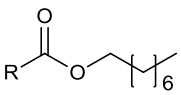
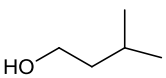
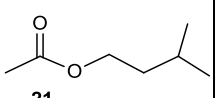
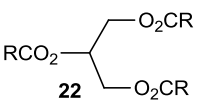
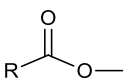
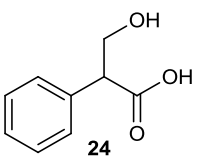
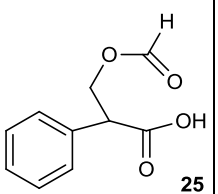
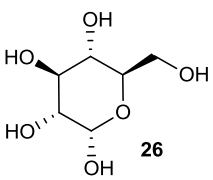
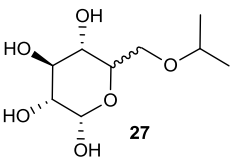
In general, addition of iodine to a triple bond is a known reaction, but typically the iodine has originated from I_2. One-pot reactions, in which iodide has originated from X^+I^- salts are unknown. Unexpectedly, by using the novel tool reported here, (E)-2,3-di-iodo-prop-2-en-1-ol (**11**) could be prepared in the dark from propargyl alcohol (**10**) using dry NaI as an iodine source and achieving a 60% yield. The absolute structure has been verified by X-ray crystallography and will be reported elsewhere.

The ring-opening reactions of a saturated heterocyclic ring containing ether bonds depend on the ring size, since small strained rings such as oxirane and oxetane are rather easily opened under acidic conditions. In addition, hundreds of literature references are available describing the preparation of 5-halopentanol from tetrahydrofurane (THF), but there are only a couple of reports in which 6-halohexanol has been prepared directly from tetrahydro-*2H*-pyran (THP), and only one of them actually describes the synthesis of 6-iodohexanol (**13a**) from THP using NaI and toxic BF_3-etherate.[7] The reaction opening 1,4-dioxane to 2-(2-Iodo-ethoxy)-ethanol (**13b**) has not previously been described. Actually, none of the above mentioned ring-opening reactions with X^+Y^- (Y^- = Br^- or I^-) salts over activated acidic solid supports have been reported previously.

Direct substitution of a primary, secondary or tertiary hydroxyl group with any kind of alkyl chain by a halogen (Cl^-, Br^- or I^-) moiety is a highly unfavourable process, since the OH group is a poor leaving group due to its high pK_a value. Typically this substitution reaction (OH to halide) is achieved by using a large excess of halide as the starting reagent or by first changing the hydroxyl group to a better leaving group e.g. via tosyl addition and then changing it to halide. Until now, there have been no reports of direct OH substitution to iodine under the present conditions. As an example, octyl iodide (**15a**) was prepared from octanol (**14a**) using 2 eq of dried NaI and 12-iodo-dodecanoic acid (**15b**) from 12-hydroxy-dodecanoic acid (**14b**) using 2.15 eq of dried NaI with 43% and 71% isolated yields, respectively. For comparison, when the highly reactive $ZrCl_4$/NaI system[8] is used as a reagent for octyl iodide (**15a**) preparation from octanol (**14a**), excellent 97% yield has been achieved. This is a much greater yield than with our reported method, but conversely, there are no reports in the literature of any method for single-step preparation of ω-iodo-alkanoic acids from ω-hydroxy-alkanoic acids.

From the scientific point of view, the above-mentioned reactions are considered beneficial and advantageous producing various end products, starting materials and intermediates e.g. for medicinal chemistry purposes. However, if one considers the procedure in terms applications to green chemistry, one of the key reactions in our system is esterification of acids with alcohols. In particular, esterification of free fatty acids in methanol at room temperature achieve quantitative yields to the corresponding methyl esters, which are the main components of biodiesel.

Table 1. Overview of the reactions

Substrate	Conditions[a] Yield[b]	Product	Substrate	Conditions[a] Yield[b]	Product
 **4**	r.t. 10-15 min. 65% (**5a**) 54% (**5b**)	 **5a** X=H **5b** X=D	 **6**	r.t. 2 h 45%	 **7**
4	40-50°C, overnight 51% (**8a**) 45% (**8b**)	 **8a** R = Me **8b** R = Bu	**6**	r.t., overnight 89%	 **9**
 **10**	65°C, overnight 60%	 **11**	 **12a**, X=CH_2 **12b**, X=O	reflux, overnight 68% (**13a**) 33% (**13b**) 30% (**13c**)	 **13a**, X=CH_2, Y=OH **13b**, X=O, Y=OH **13c**, X=CH_2, Y=I
 **14a**, n =7, X=H **14b**, n=10,X=CO_2H	85-100°C, 5 h to overnight 43% (**15a**) 71 % (**15b**)	 **15a**, n =7, X=H **15b**, n=10,X=CO_2H	 **16**	r.t., 15 min-1 h 99%	 **17**
14b	85°C, 4 h 70%	 **18** n=10	**14a**	85-100°C, overnight 40% (**19a**) 41% (**19b**)	 **19a**, R=Me **19b**, R=Et
 **20**	50°C, 2 h (100% conversion) 64%	 **21**	 **22**	68°C, overnight approx. 90%[c]	 **23**
 **24**	115°C, overnight 56%	 **25**	 **26**	85°C, overnight 83%	 **27**

[a]In the table only the reaction time and temperature has been highlighted, detailed experimental procedures and conditions can be found in the supporting info; Dowex® H^+ (D^+ for **5b**) ion exchange resin was used in all reactions reported in this table, some of the reactions can be performed also using either 11-Amino-1-hydroxyundecane-1,1-diylbisphosphonic acid, Diphonix® or Amberlyst® H^+ ion exchange resin instead of Dowex®, [b] isolated yields, [c] it was impossible to measure the exact yield because the real fatty acid composition of **22** was not known, r.t. = room temperature, oven dried NaI was used in all reactions.

There are several methods for direct esterification of fatty acids to the corresponding esters by alcohols based on both homogenous catalysis, such as p-TosOH[9] or H_2SO_4 catalysis[10] or I_2[11], and heterogeneous catalysis: sulphated ZrO_2–TiO_2 systems[12], montmorillonite[13], and 12-tungstophosphoric acid anchored to SBA-15[14], have been developed but all these methods require elevated temperatures (40°C - 100°C) and long reaction times (4h – 48h). One can conduct esterification at room temperature with ionic liquid[15], but the typical reaction times are 3-5h, the yields of fatty acid esters are lower (e.g. oleic acid methyl ester, reported yield is 88%) and product isolation is more complicated when compared with the method

described here. It is possible to perform quantitative esterification of fatty acids to their methyl esters at 20°C with highly reactive esterification agents, such as diazomethane[16] or PPh_3-I_2 reagent[17]. The closest results compared to the method described here have been obtained with cerium(IV) ammonium nitrate reagent[18] with a 2 h reaction time and 99% yield, but product isolation is more complex.

The mildest reaction conditions with which to obtain the quantitative esterification of oleic acid (**16**) to its methyl ester (**17**) was achieved within 15 minutes, when **16** was stirred with 0.1 eq of dried NaI in dry MeOH at 17°C. When common MeOH (not dried) was used as the solvent, the quantitative esterification was observed after 1 h with stirring at room temperature. We noticed that if more NaI (0.2-2 eq) was used in the reaction, this generally reduced the reaction time. The same reaction was also performed without NaI at room temperature, but in that case approx. 20% of oleic acid methyl ester (**17**) was formed. In comparison, the same reaction was performed using conc. H_2SO_4 as catalyst but in this case altough the conversion to **17** was excellent after 2 h reaction time, the ^{1}H NMR spectrum indicated the formation of approx. 10% of side products. In addition, direct esterification with bulkier alcohols, such as isopropanol is possible with the tool reported here, since 12-hydroxy-dodecanoic acid isopropyl ester (**18**) was obtained in a straightforward manner from **14b** with 70% isolated yield by refluxing **14b** for 4 h in 2-propanol and using 0.2 eq of NaI as catalyst.

Based on the above experience, the method was then also tested for prepairing biodiesel (**23**). Nowadays biodiesel is commonly prepared from triglycerides derived from plant matter, such as vegetable oils using transesterification reaction. The problems in the production processes are related to saponification ($RCO_2H + NaOH \rightarrow RCO_2Na + H_2O$)[19], which complicates the product separation, and the presence of water ($RCO_2Me + H_2O \rightarrow RCO_2H + MeOH$)[19] which lowers the yields. Here, biodiesel was prepared from fatty acid triglycerides (**22**) on a 10 ml scale by using cooking oil samples collected from restaurants by a local company. Most of the water was separated and the material was used without further treatments. Typically, approx. 90% yields and >95% purity (see Table 1 and ^{1}H NMR spectrum of product **23** and starting material **22** in the Supplementary Information) were obtained with this newly developed method.

We have demonstrated here how oleic acid can be effectively esterified to its methyl ester under extremely mild conditions and how a real cooking oil sample can be converted into biodiesel. We therefor considered another possibility, does this method work in the reverse direction: can alcohol be esterified to its corresponding ester in an excess of carboxylic acid? This proved to be possible, and as an example, isopentanol (**20**) can be esterified to isopentyl acetate (**21**) in acetic acid (1.9 eq) without any solvent by stirring a mixture of isopentanol (**20**), acetic acid (1.9 eq) and dried Dowex® H^+ form for 2 hours at 50°C using 0.1 eq of dried NaI as the catalyst. Complete (100%) conversion to isopentyl acetate (**21**) was observed according to the ^{1}H NMR spectrum, but because of the high volatility of **21**, the isolated yield was "only" approx. 64%. As a comparison, quantitative conversion has been reported for the preparation of isopentyl acetate (**21**) starting from acetic acid and isopentanol (**20**) at 50°C by using lipase as a catalyst. However, the reported method needs ionic liquid/solid phase system as a reaction medium[20] and in general, the methods reported in the literature for preparation of **21** require either higher temperatures and/or some kind of solvent systems. In addition, when *tert*-butanol, acetic acid (approx. 8 eq), dried Dowex® H^+ form and 0.6 eq of dried NaI were stirred for 30 minutes at 80°C; the ^{1}H NMR spectrum indicated that approx. 28% conversion to *tert*-butyl acetate had occurred.

Another possibility for prepairing esters by the method reported here is to add carbonitriles to alcohols in the presence of water. As an example, octanol (**14a**) was refluxed overnight with dried Dowex® in common (not dried) acetonitrile or propionitrile, octyl acetate (**19a**) and octyl propionate (**19b**) were isolated with 40% and 41% yields, respectively (without any kind of reaction optimizations).

The present tool also makes it possible to use a formyl group as a nucleophile and as an example, the novel compound, 3-(formyloxy)-2-phenylpropanoic acid (**25**) was prepared from tropic acid (**24**) by stirring it in dry DMF overnight at 115°C using 1 eq of NaI. Product **25** was isolated with 56% yield.

Last but not least, we describe an example of selective etherification of a primary hydroxyl group ($-CH_2OH$) over the secondary groups of D(+)-glucose (**26**) in one pot. Without the protection of secondary hydroxyl groups, product **27** was isolated with a high 83% yield as a pair of isomers (ratio 1:2). Traditionally, the selective substitution of a primary OH group from carbohydrates requires several protection and deprotection steps, but by using our novel tool such protection is not needed. We have preliminary results for another kind of substituent attached selectively to the primary hydroxyl group of sugar with the method described here, but this will be reported elsewhere in the future.

In summary, we conclude that the reported tool satisfies the essential criteria of green chemistry. However, the possible formation of I_2 and HI must be considered when planning reactions to be made with this tool. When NaI was used as catalytic amounts in the reactions there was usually no problem, but when it was used as reagent the crude reactions usually were dark in color probably due to the formation of I_2 and possibly HI, and they needed to be neutralized by sodium thiosulfate [see as an example the detailed procedure for the synthesis of 2-(2-iodo-ethoxy)-ethanol (**13b**) in Supplementary Information page S5]

Proposed reaction mechanisms

In general, the exact reaction mechanism is difficult to determine, even for simple chemical reactions. Typically the mechanism is based on several routes or their combinations, such as bond enthalpy and polarization, resonance structures, sterical effects and/or the entropy of the reactions. In this reaction system, one of the key features is sterical requirements, since the chain ends are more reactive in preference to other more hindered positions. Moreover, the H^+ form solid material favours proton transfer reactions from the solids to reagents, since ionic sodium iodide is less soluble in alcohols and polar aprotic solvents than the corresponding acid, e.g. HI. Most of the reactions illustrated in Table 1 can be explained based on the sterical requirements and *in situ* formed hydrogen iodide, which is highly effective protonation agent (the pKa value for HI is ca. -10)[21] for the generation of leaving groups and the counter anionic iodide which is a good nucleophile with this solid system. Even the catalytic esterification between acids and alcohols can possibly be attributed to the formation of HI, since the highly reactive RCOI intermediate is formed via a stable $RC{\equiv}O^+$ carbocation from RCO_2H after water cleavage.

In the case of esterification of alcohols with carbonitriles (RCN), the reaction is initiated with proton transfer from the

solid material to a cyanide moiety and a reactive $R^+C=NH$ compound is obtained. This intermediate reacts readily with the excess of alcohol and water (1 eq) to the enthalpy favoured ester product. Actually, the formation of trans-1,2-diiodoethene derivatives (as compound **11**) and formylation of alcohols are the only products that cannot be explained directly in terms of the above discussed reaction mechanism. In the first case, we propose that I_2 molecules are the species reacting with the triple bond and in the latter case, one possible explanation may be a reactive ICHO formed from Me_2NCHO (dimethyl formamide) after alcohol addition leading to end product **25**.

Conclusions

We have presented and demostarated a novel green chemistry synthetic tool with which to prepare acid catalysed addition and substitution reactions under mild reaction conditions. In the reported tool, the salt form iodide anion over dry H^+ form solid material acted either as a reagent or as a catalyst. The method makes it possible to conduct straightforward synthesis of a wide variety of compounds, like esters, tertiary iodides or ethers, 1,2-diiodoethene derivatives, iodoalkanols and sugar derivatives in a one-pot procedure without any protection steps but still with excellent conversions. The tool will be advance for everyone needed synthesis in their work and is definitely an interesting starting point for finding novel methods for the synthesis of radioiodine-labelled compounds. Finally, most of the reactions reported here were also performed using regenerated Dowex® H^+ cation exchange resin and they worked as well or even better than reactions performed with the original Dowex®.

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Notes and references

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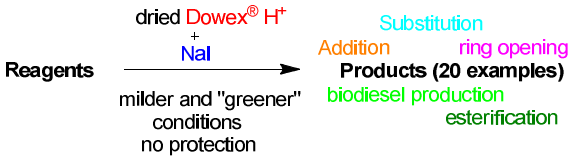
1 S.D. Alexandratos, *Ind. Eng. Chem. Res.*, 2009, **48**, 388.
2 D. Jiang, Y.Y. Wang, M. Tu and L.Y. Dai, *Chinese Chem. Lett.*, 2008, **19**, 889.
3 H. Mönkkönen, S. Auriola, P. Lehenkari, M. Kellinsalmi, I.E. Hassinen, J. Vepsäläinen and J. Mönkkönen, *Br. J. Pharmacol.*, 2006, **147**, 437.
4 P.A. Turhanen, *J. Org. Chem.* 2014, **79**, 6330.
5 S. Irifune, T. Kibayashi, Y. Ishii and M. Ogawa, *Synthesis*, 1988, 366.
6 P. Turhanen, S. Peräniemi and J. Vepsäläinen, Patent WO2012131170 (A1).
7 Z. Li. Wei-Dong, D. Wei-Guo and Z. Cheng-Han, *Org. Lett.*, 2011, **13**, 3538.
8 H. Firouzabadi, N. Iranpoor and Maasoumeh Jafarpour, *Tetrahedron Lett.*, 2004, **45**, 7451.
9 M.R. dos Santos, J.R. Diniz, A.M. Arouca, A.F. Gomes, F.C. Gozzo, S.M. Tamborim, A.L. Parize, P.A. Suarez and B.A. Neto, *ChemSusChem*, 2012, **5**, 716.
10 F-L. Wu, B.P. Ross and R.P. McGeary, *Eur. J. Org. Chem.*, 2010, 1989.
11 K. Ramalinga, P. Vijayalakshmi and T.N.B. Kaimal, *Tetrahedron Lett.*, 2002, **43**, 879.
12 D.C. Boffito, V. Crocell, C. Pirola, B. Neppolian, G. Cerrato, M. Ashokkumar and C.L. Bianchi, *J. Catalysis*, 2013, **297**, 17.
13 G.B.B. Varadwaj, S. Rana and K. Parida, *Chem. Eng. J.*, 2013, **849**, 215.
14 V. Brahmkhatri and A. Patel, *App. Catal. A.*, 2011, **403**, 161.
15 X. Li and W. Eli, *J. Mol. Catal.*, 2008, **279**, 159.
16 A.A. Singh, S.N.A. Zulkifli, M. Meyns, P.Y. Hayes and J.J. De Voss, *Tetrahedron: Asymmetry*, 2011, **22**, 1709.
17 S.P. Morcillo, L.A. de Cienfuegos, A.J. Mota, J. Justicia and R. Robles, *J. Org. Chem.*, 2011, **76**, 2277.
18 W-B. Pan, F-R. Chang, L-M. Wei, M-J. Wu and Y-C Wu, *Tetrahedron Lett.*, 2003, **44**, 331.
19 F. Ma and M.A. Hanna, *Bioresource Technol.*, 1999, **70**, 1.
20 P. Lozano, J.M. Bernal and A. Navarro, *Green. Chem.*, 2012, **14**, 3026.
21 http://www.columbia.edu/~crg2133/Files/CambridgeIA/Chemistry/AciditybasicitykPa.pdf (accessed June 23, 2014).

Graphical Abstract



Novel approach to perform organic reactions using dried Dowex® H^+/NaI system has been reported.