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Solvent and catalyst free synthesis of imidazo[1,2-a]pyridines by grindstone chemistry

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Abstract

The present communication describes the solvent and catalyst free synthesis of imidazo[1,2-a]pyridines in excellent to nearly quantitative yields from 2-aminopyridines and a wide variety of ω-bromomethylketones using a grindstone procedure at 25-30 °C for 3-5 min. This green strategy has several noteworthy advantages such as wide spread substrate scope, short reaction times, water work up and the products do not require any chromatographic purification. Further, it is simple to perform, highly economical and therefore the process is easy to scale up.

Keywords

2-aminopyridines; ω-bromomethylketones; imidazo[1,2-a]pyridines; solvent and catalyst free; grindstone chemistry

Introduction

Imidazopyridines are considered as privileged nitrogen-fused heterocycles because of their potential applications in biology [1]. Among various imidazopyridines, the imidazo[1,2-a]pyridines have received substantial attention of the pharmaceutical industry owing to their promising medicinal applications viz., anticancer, antiviral, antipyretic, analgesic, anti-inflammatory, anticonvulsant, antifungal, anthelmintic, antibacterial, anti-protozonal, antiulcer, antiepileptic, antiparasitic and antituberculosis properties [2-12]. These compounds also serve as cyclin-dependent kinase (CDK) inhibitors [9], benzodiazepine receptor agonists, *β*-amyloid formation inhibitor, calcium channel blockers [10], cardiotonic agent [7] and $GABA_A$ receptor modulators [13-17]. More importantly, imidazo[1,2-a]pyridine nucleus is a key structural unit in many commercially available pharmaceutical drugs including zolimidine (I) [18], zolpidem (II) and alpidem (III) [19], GSK812397 (IV, optically active drug) [20], Rifaximin (V) [21], olprinone (VI) [22], necopidem (VII) and saripidem (VIII) [23] (Figure 1). Besides, these compounds are valuable building blocks in organometallic chemistry and materials science [24, 25].

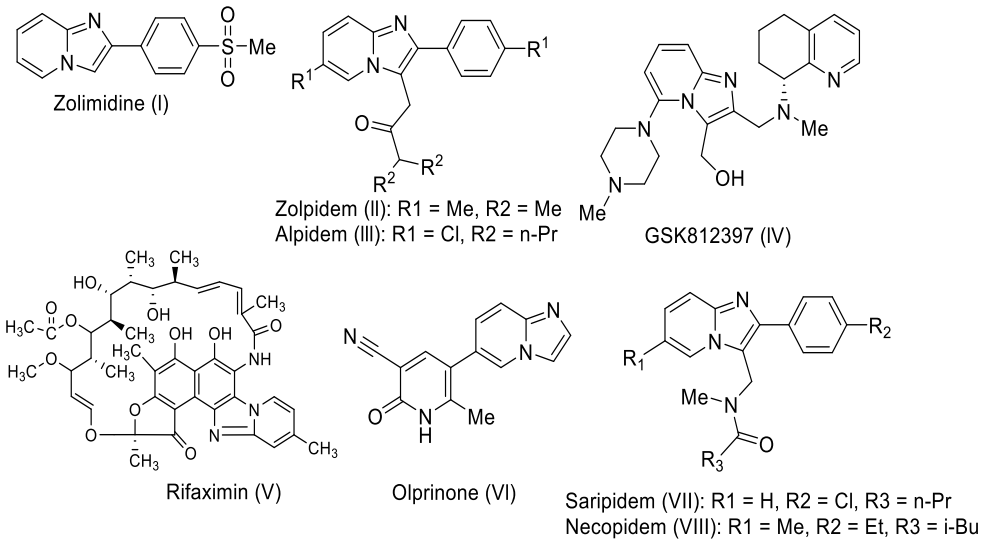
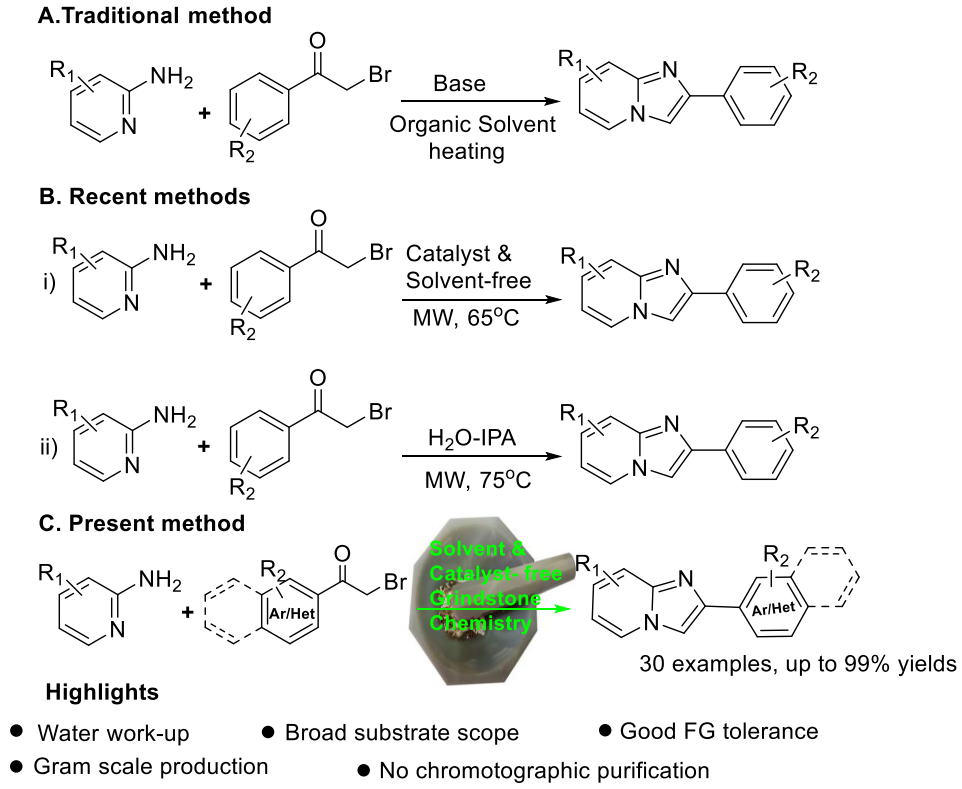


Figure 1. Selected examples of Imidazo[1,2-a]pyridine-based drugs.

In view of their broad based utility, extensive research has been conducted and a huge number of synthetic strategies have been reported for the synthesis of imidazo[1,2-*a*]pyridines [26]. Among the developed synthetic routes, the reaction of 2-aminopyridines with α-haloketones is the most common procedure for the synthesis of imidazo[1,2-*a*]pyridines in both laboratory and industrial scale. This traditional synthesis has been conducted in the presence of various catalysts such as neutral Al_2O_3, $NaHCO_3$, K_2CO_3, NaI, $TiCl_4$ etc., in organic solvents at high temperature [27a-j] and polar organic solvents [27k]. Further, the same reaction has been examined under microwave irradiation [28]. For instance, water and isopropanol mediated catalyst-free microwave assisted synthesis at 75°C has been developed by Rao [28a] *et al*.; Lin *et al*. reported the solvent and catalyst-free synthetic route for imidazo[1,2-*a*]pyridines under microwave irradiation at 65°C [28b]. Despite these developments, there are still some drawbacks such as narrow substrate scope, use of transition metal catalysts and toxic organic solvents, harsh reaction conditions, lengthy reaction times, overheating of substrates, use of expensive techniques, tedious work up process involving the use of large excess of organic solvents and the products require column chromatographic purification. Therefore, the development of improved economic, green and sustainable synthetic routes that can avoid or minimize the use of toxic solvents and catalysts for the preparation of imidazo[1,2-a]pyridines is still highly desirable in pharmaceutical industries.

Based on the environmental concerns in pharmaceutical industry, grindstone chemistry (GSC) recently has emerged as a promising green technique to perform solvent-free solid-state reactions in various fields of chemistry just by grinding solid reactants together with a mortar and pestle [29-32]. This

technology meets the concept of “benign by design” because it does not need any specialized equipment and is therefore economical, ecological and simple to carry out in any laboratory [33]. However, to date there are no reports on solvent and catalyst-free syntheses of imidazo[1,2-a]pyridines at room temperature using grindstone chemistry.



Scheme 1. Methods for the synthesis of imidazo[1,2-a]pyridines

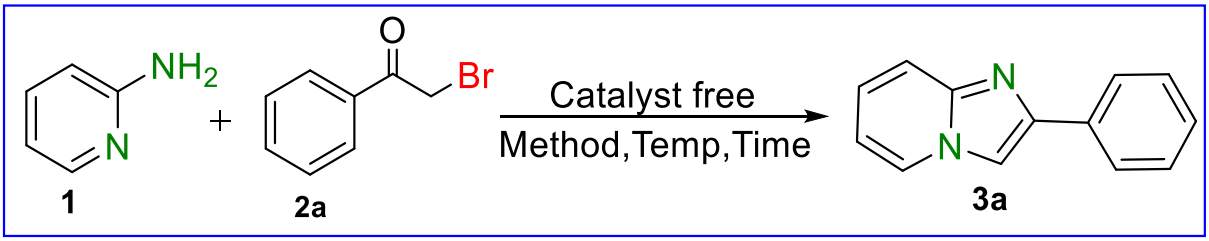
In continuation of our interest in the development of solvent-free solid-state reactions using grind stone technology for the synthesis of pharmaceutically active compounds (PhACs) [34], we demonstrated herein, a rapid, more efficient, green and sustainable synthetic route for the synthesis of a series of imidazo[1,2-a]pyridines in nearly quantitative yields by simply grinding of 2-aminopyridines and a wide variety of ω-bromomethylketones using mortar and pestle at 25-30°C for 3-5 min under solvent and catalyst free conditions (Scheme 1C).

Results and Discussion

Encouraged by the improvements in the development of green synthetic strategies for the synthesis of clinically important imidazo[1,2-a]pyridines,[28] we aimed to develop an easy, low cost, highly efficient, scalable, clean and green procedure for the synthesis of imidazo[1,2-a]pyridines (3). For this purpose, initially, we ground the model substrates, 2-aminopyridine (1a) (5.0 mmol) and ω-bromoacetophenone (2a) (5.0 mmol) by adding two drops of water at 25-30 °C for7 min and resulted in 80% yield of 2-phenyl imidazo[1,2-a]pyridine (3a) (entry 1, Table 1). Further, the same reaction was repeated by employing a variety of solvents (two drops) like ethanol, isopropanol (IPA), poly (ethylene glycol) (PEG) and glycerol at 25-30 °C for 7-10 min. This solvent-drop grinding (SDG) method revealed that the reaction proceeded smoothly and afforded moderate to good yields of desired product, 3a that ranged from 60% to 85% (Table 1, entries 2-5). To improve the yield of 3a, the same reactants, 1a and 2a were ground together under solvent and catalyst free reaction conditions at 25-30 °C. To our delight, the desired product, 3a was obtained in nearly quantitative yield, 99% in a short reaction time (3 min) (Table 1, entry 6). Next, we examined the same reaction under ultrasound irradiation (USI) in different solvents like water, ethanol, IPA, PEG and glycerol in the absence of catalyst at 55-60°C for 45-60 min. From this study, it was noticed that the solvents, ethanol and IPA provided moderate yields of 3a, 75% and 78%, respectively. The other solvents, water, PEG and glycerol resulted in lower yields of product 3a (Table 1, entries 7-11) which may be due to the poor solubility of reactants. From the above observations, it was concluded that the grinding of reactants under solvent and catalyst free reaction conditions was superior when

compared to both solvent-drop grinding (SDG) method and ultrasound irradiation (USI) method in giving almost quantitative yield of product **3a** in a short period of time at 25-30°C (Table 1).

Table 1. Optimization of the reaction conditions



Entry	Conditions		Time (min)	Isolated yield (%)[d]
	Solvent	Method		
1	Water (2 drops)	SDG[a]	7	80
2	Ethanol (2 drops)	SDG[a]	7	85
3	IPA (2 drops)	SDG[a]	7	85
4	PEG (2 drops)	SDG[a]	10	75
5	Glycerol (2 drops)	SDG[a]	10	60
6	**Solvent-free**	**GSC[b]**	**3**	**99**
7	Water (5mL)	USI[c]	45	40
8	Ethanol (5mL)	USI[c]	30	75
9	Isopropanol (5mL)	USI[c]	30	78
10	PEG (5mL)	USI[c]	60	50
11	Glycerol (5mL)	USI[c]	60	50

Reactions conditions: 2-aminopyridine (1a) (5.0 mmol) and ω-bromoacetophenone (2a) (5.0 mmol), performed under specified conditions without any catalyst. [a] SDG: solvent-drop grinding at 25-30°C. [b] **GSC: grindstone chemistry at 25-30°C under solvent-free conditions.** [c] USI: ultrasound irradiation at 55-60°C in different solvents. [d] Isolated yields.

To study the efficiency and applicability of the above optimized procedure (Table 1, entry 6), the scope of the reaction of diversely substituted ω-bromomethylketones (2) and 2-aminopyridines (1) was investigated (Table 2). 2-Aminopyridine (1a) reacts with ω-bromoacetophenone (2a) to give the corresponding 2-phenylimidazo[1,2-a]pyridine (3a) in 99% yield. ω-bromoacetophenone bearing activating groups, 4-Me (2b), 4-OMe (2c) and 3-

OMe (2c) at $4^{th}/3^{rd}$ position of the aromatic ring showed excellent reactivity with the nucleophilic partner, 2-aminopyridine (1a) to afford the 2-aryl imidazo[1,2-a]pyridines, 3b, 3c and 3d in nearly quantitative yields, 99%, 99% and 98%, respectively. 2-Aminopyridine (1a) reacted well with ω-bromoacetophenone containing deactivating groups such as 4-Br (2e), 3-Br (2f), 4-Cl (2g), 3,4-dichloro (2h) and 4-F (2i) at different positions of the aromatic ring to produce the desired products, 3e-3i in excellent isolated yields that ranged from 95-99%. ω-bromoacetophenones 2i-2l, bearing strongly deactivating groups, 4-CN(2j), 4-NO_2 (2k), 3-NO_2 (2l) at $4^{th}/3^{rd}$ position of the aromatic ring underwent the reaction with 2-aminopyridine (1a) to obtain the products, 3j, 3k and 3l in excellent to almost quantitative yields, 99%, 99% and 97%, respectively. Interestingly, the present procedure worked well for hindered ω-bromo-2-acetonaphthone (2m) and **ω**-bromo-4-phenylacetophenone (2n) and heteroaromatic 3-(bromoacetyl)coumarin (2o) producing the corresponding products 3m,3n and 3o in excellent isolated yields. Similarly, ω-bromoacetophenones with activating/deactivating groups, 2a-2l exhibited excellent reactivity with 2-amino-4-methylpyridine (**1b**) to produce the desired products 3p-3aa in excellent to nearly quantitative yields that ranged from 94-99%. The absolute structure of **3u** was determined by X-ray crystallography (Figure 2) and it is monoclinic with $P2_1/c$ space group of one molecule in the asymmetric unit (Z = 4). Further, it was also noticed that the sterically hindered ω-bromo-2-acetonaphthone (2m) and **ω**-bromo-4-phenylacetophenone (2n) and heteroaromatic 3-(bromoacetyl)coumarin (2o) were underwent the reaction with 2-amino-4-methylpyridine (1b) and provided the corresponding products, 3ab-3ad in good isolated yields. From the above study, it was concluded that the developed green strategy was successfully

applied on structurally diversified ω–bromomethylketones and 2-aminopyridines and found that all of the substrates were well tolerated under the optimized reaction conditions.

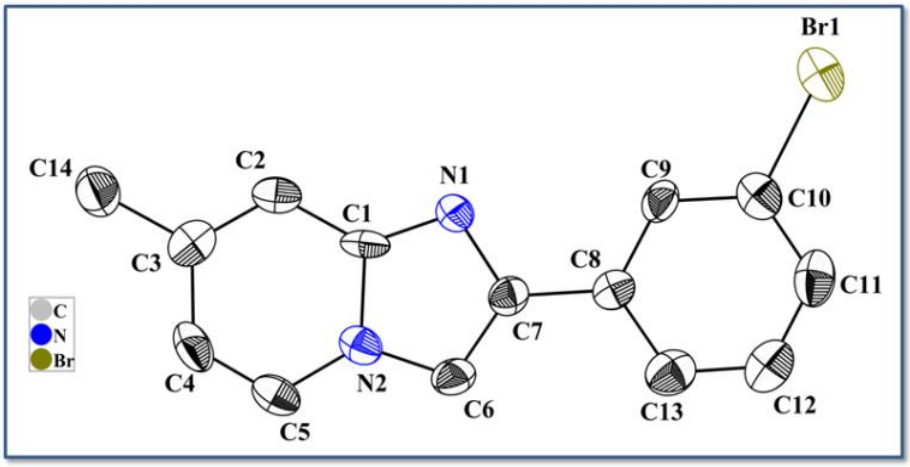


Figure 2. ORTEP diagram of compound 3u (50% probability).

Encouraged by the above results, the scalability of the process was then tested by the reaction between 2-amino-4-methylpyridine (**1b**) and ω-bromo-3-bromoacetophenone (2f) in different gram scale reactions, 5, 10, 15, 20 and 25 grams under the optimized procedure. The yields of product **3u** were obtained as 99%, 99%, 98%, 97% and 97% (Figure 3). It is worthy to state that the solvent and catalyst free grindstone procedure is a promising greener alternative for the multi gram-scale production of imidazo[1,2-a]pyridines (3).

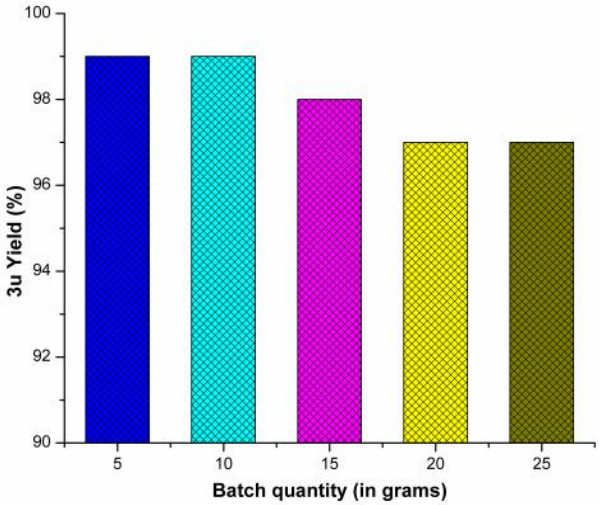
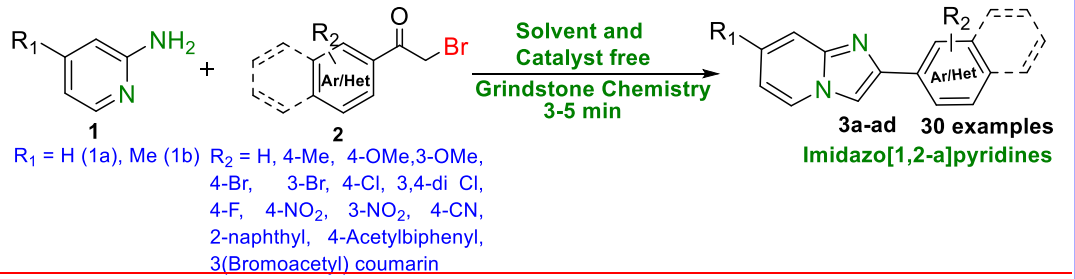
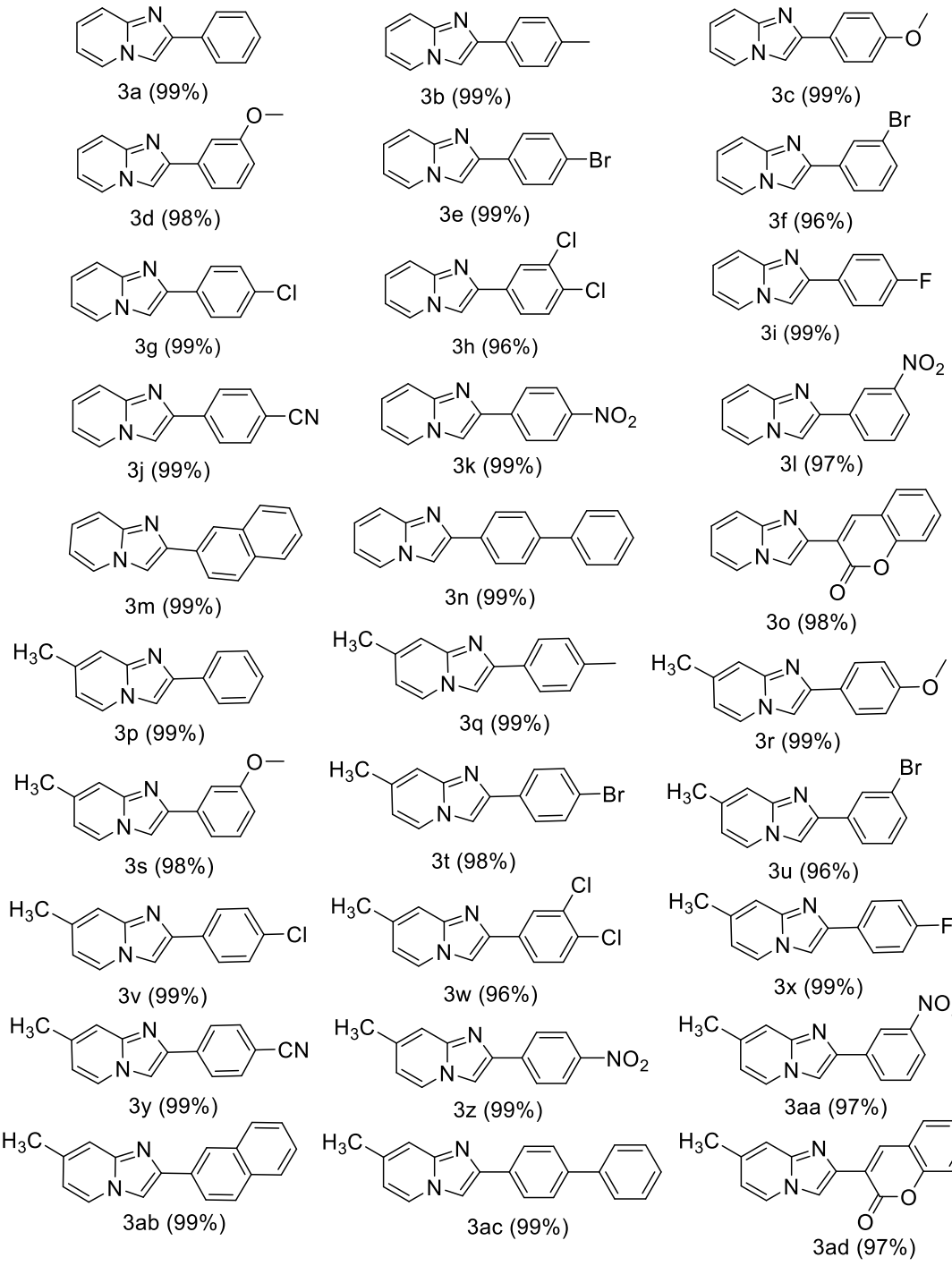


Figure 3. Gram-scale synthesis of 3u.

Table 2. Synthesis of a series of imidazo[1,2-a]pyridines(3) using grindstone chemistry.



R_1 = H (1a), Me (1b) R_2 = H, 4-Me, 4-OMe,3-OMe, 4-Br, 3-Br, 4-Cl, 3,4-di Cl, 4-F, 4-NO_2, 3-NO_2, 4-CN, 2-naphthyl, 4-Acetylbiphenyl, 3(Bromoacetyl) coumarin



Reactions conditions: 2-aminopyridines (1) (5.0 mmol) and ω-bromoacetophenone (2) (5.0 mmol); All reactions performed under solvent and catalyst free conditions using grindstone chemistry at 25-30°C.

Conclusions

A facile, green and ecologically favourable grindstone procedure has been established for the preparation of clinically imperative 2-substituted imidazo[1,2-a]pyridines from 2-aminopyridines and a wide variety of ω-bromomethylketones under solvent and catalyst free conditions at 25-30°C. Broad substrate scope, operational simplicity, water work-up, no organic waste generation, excellent to nearly quantitative yields in a short reaction times, products free from chromatographic purification and gram scale feasibility are the remarkable features of the present method. Hence, the developed synthetic route is more economical and greener alternative to the reported procedures for the synthesis of imidazo[1,2-a]pyridines.

Experimental

See Supporting Information File 1 for full experimental data.

Supporting Information

Supporting Information File 1: Check CIF of compound 3u (PDF)

Supporting Information File 2: Crystallographic data of compound 3u in CIF format (CCDC 1986012).

Supporting Information File 3: Experimental procedures, characterization data and copies of ^{1}H NMR, HRMS and LCMS spectra of title compounds (3).

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