JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00717 • Publication Date (Web): 08 May 2019

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

A Microwave-Assisted SmI_2-Catalyzed Direct *N*-Alkylation of Anilines with Alcohols

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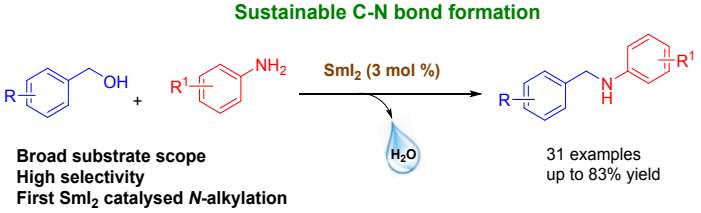


ABSTRACT: A new protocol for the alkylation of aromatic amines has been described using alcohols in presence of SmI_2 as catalyst with the generation of water as the sole byproduct. The reaction proceeds under MW conditions and selectively generates monoalkylated amines. This protocol features broad substrate scope and good functional-group tolerance with moderate to high yields.

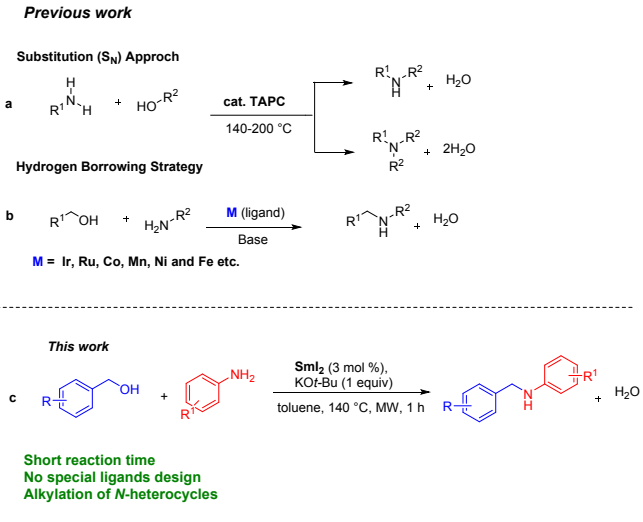
The direct construction of C-N bond is of immense interest due to important application of amine functionality[1]in pharmaceuticals, agrochemicals, material chemistry and chemical industry.[2] Therefore, development of new selective and efficient methodologies for the monoalkylation of amine has gained significant interest in both academic and industrial communities.

In this direction, several methods have been successfully developed for the alkylation of amine, which includes the reactions of amines with alkyl halides,[3] reductive alkylation[4] and electrophilic amination[5] reactions. In particular, the activation of alcohols under mild conditions for *N*-alkylation have been identified as a more suitable methods,[6] which are commonly performed by ruthenium[7] or iridium complexes[8] and less often by other transition metal complexes.[9] Recognizing the potential of this transformation, several groups have pursued various strategies for the direct construction of C-N bond.[10] In 2011, selective *N*-mono- and dialkylation of amines with alcohols by using non-metal-based acid–base catalysis were successfully achieved by Saito and co-workers which involves substitution (S_N) at the alcohols sp^3 carbon atom bearing the hydroxyl group (Scheme **1a**).[11a] Recently, Kempe[11b](Co catalyst), Beller,[12] and Milstein[13](Mn pincer complexes) demonstrated the convenient protocol for alkylation of amines by borrowing-hydrogen or hydrogen-autotransfer (BH/HA) approach. Base-promoted direct alkylation of amines with alcohols under transition-metal-free conditions was reported. However, longer reaction time and excess of base were necessary.[14] More recently, an elegant example of nickel-catalyzed direct alkylation of amines using benzyl alcohols was described by Banerjee and co-workers.[15a] In 2014, Barta and co-workers reported the first example of a direct amination of alcohols catalyzed by an iron complex[15b] through the borrowing hydrogen strategy (Scheme **1b**).

Despite these achievements, these methods have shortcomings due to expensive metal complexes, requirement of stabilizing ligands such as PN5P ligand, alanine-triazole ligand, PNP pincer, pyridine-based PNNH pincer and NHC.[6a, 10b, 16] Thus, the there exists a need for developing easily accessible and inexpensive catalytic systems for monoalkylation of amines is desirable.

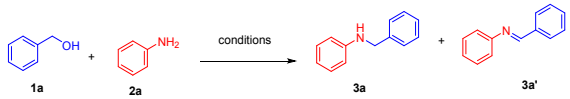
In the last decades, samarium diiodide (SmI_2) catalyst has gained considerable interest due to various useful synthetic applications in organic chemistry.[17a] However, the use of SmI_2 is limited to reductive manipulations of functional groups and reductive couplings to make C−C bonds.[17] Herein, we are disclosing a new protocol for monoalkylation of various amines with alcohols in presence of samarium diiodide (Scheme **1c**). To the best of our knowledge, this is the first demonstration of monoalkylation of amines with alcohols by utilizing samarium diiodide (SmI_2) as catalyst.

Scheme 1.Various Synthesis Strategies for the *N*-alkylation of amines



As a model system, the SmI_2-catalyzed alkylation of aniline (**2a**) with benzyl alcohol (**1a**) was optimized (Table 1). With the use of 3 mol % of SmI_2 catalyst for the reaction of **1a** (1.5 mmol) with **2a** (1.0 mmol) in presence of KO*t*-Bu (1.0 mmol) in toluene at 140 °C, the reaction was slow. Only 38% and 65% conversion of **3a** was obtained when the reaction was carried out for 24 and 36 hours respectively (Table 1, entry 1, 2). Interestingly, when the reaction was performed under microwave irradiation (Table 1, entry 3), it resulted in complete conversion of the starting materials to afford **3a** in 81% yield after 1 h. Encouraged by these results, we further investigated other reaction parameters, such as solvent, base, and substrate ratio (see the Supporting Information). Initially, solvent screening showed that etherate solvent such as THF gave a mixture of products **3a** and **3a'** in equal ratio (Table S1, entry 4, SI). Whereas, other solvents such as DMF and methanol gave inferior results (see Table S1, Supporting Information). Further, exploring the effect of bases, potassium *tert*-butoxide gave best results under MW conditions (Table S2, SI). Surprisingly, when the reaction was carried out with sodium hydroxide as base, it yielded **3a** in moderate yield and **3a'** as major product (Table 1, entry 4).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	solvent	base	time	[b]conversion (%) 3a	3a'
1	SmI_2(3)	toluene	KO*t*-Bu	24 h	38	52
2	SmI_2(3)	toluene	KO*t*-Bu	36 h	65	35
3[c]	**SmI_2(3)**	**toluene**	**KO*t*-Bu**	**1 h**	**89 (81)**	**0**
4[c]	SmI_2(3)	toluene	NaOH	1 h	31	58
5[c]	SmI_2(3)	toluene	KO*t*-Bu	40 min	71	18
6[d]	SmI_2(3)	toluene	KO*t*-Bu	1 h	87	0
7[e]	SmI_2(3)	toluene	KO*t*-Bu	1 h	27	62
8[c,f]	SmI_2(3)	toluene	KO*t*-Bu	1 h	74	13
9[c]	SmI_2 (1.5)	toluene	KO*t*-Bu	1 h	61	24
10[c]	SmI_2(5)	toluene	KO*t*-Bu	1h	89	0
11[c]	-	toluene	KO*t*-Bu	1 h	11	
12[c]	SmI_2(3)	toluene	-	1h	0	0

[a]Reaction conditions: (1.5 mmol) benzyl alcohol,(1.0 mmol) aniline, (1.0 mmol) base, 3 mL solvent and SmI_2 (0.1 M solution in THF) at 140 °C (oil bath) for 24 and 36 h respectively in a Schlenk tube. [b]Conversion was determined by GC analysis using biphenyl as internal standard. The value in parentheses is the yield of the product **3a**.[c]Reaction was performed in microwave at 140 °C. [d]Reaction was performed in microwave at 150 °C. [e]Reaction was performed in microwave at 110 °C. [f]4 Å molecular sieves was added.

Other inorganic and organic bases proved to be comparatively inefficient for this transformation (see the Supporting Information). The reaction failed to obtain the desired product in absence of a base (Table 1, entries 12).When the reaction time was reduced to 40 min, the conversion yield of product decreased to 71% (Table 1, entry 5). When the influence of temperature was tested; it was found that increase of temperature (150 °C) did not improve the yield. When the reaction was carried out at 110 °C, imine **3a'** was formed as a major product (entries 6-7, Table 1) probably due to the deceleration of imine reduction. In the presence of 4 Å molecular sieves, the yields were considerably lower, signifying that the presence of water increases the rate of reduction (Table 1, entries 8).[18] When the catalyst loading was reduced to 1.5 mol %, it resulted in decrease of yield of **3a** (Table 1, entry 9). However, no improvement was observed with higher catalyst loading (Table 1, entries 10). In addition, reaction provided very less yield in absence of catalyst (Table 1, entries 11).

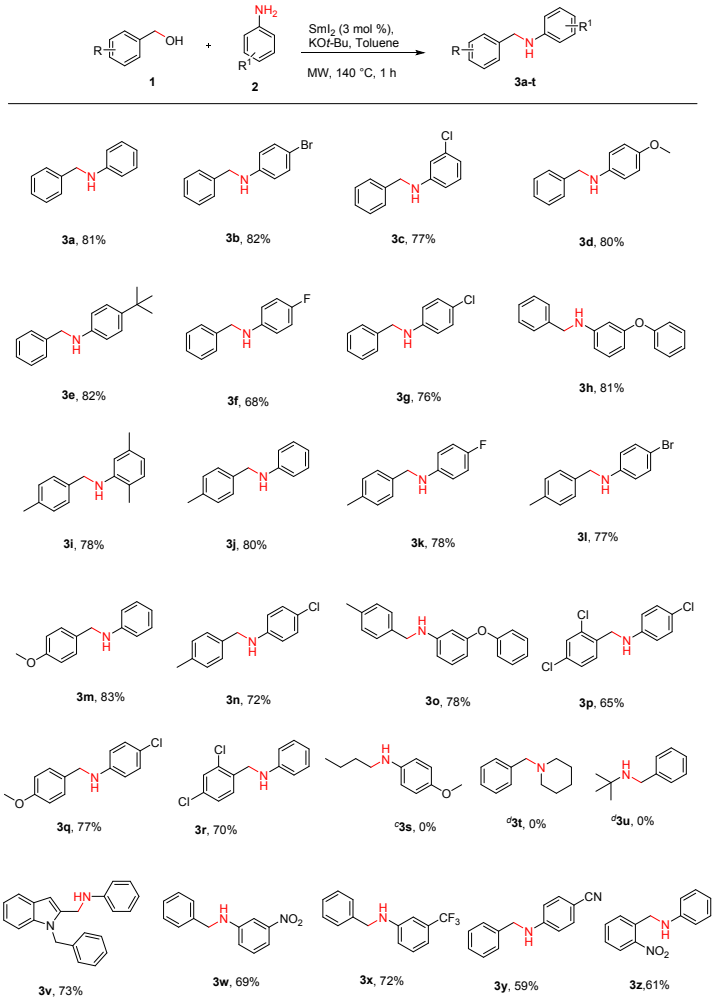
With the optimized reaction conditions in hand, we studied the scope of this new catalytic protocol for the alkylation of amines with benzylic alcohols (Table 2). Both, electron donating and electron withdrawing substituents on benzyl alcohols and anilines are well-tolerated, to achieve the desired products in good to high yields under MW irradiation. First, we tested the reactions of benzyl alcohol with various substituted anilines, and it was observed that functionalities such as methoxy, methyl, *t*-butyl and halide as well as electron-withdrawing substituents on the aryl ring were well tolerated under the reaction conditions to furnish the corresponding products in 59−82% yields. As expected, 3-phenoxyaniline also underwent *N*-monoalkylation to give the desired product in 81% yield (**3h**). In contrast, 4-fluoroaniline led to lower yield of **3f** along with the formation of imine (12% yield) as a byproduct. Next, substituted anilines were alkylated with various benzyl alcohols to show the method variability (Table 2). Again, a notable functional group tolerance was observed. 4-methoxy benzyl alcohol was found to be the suitable substrate for the SmI_2-catalysed reaction to afford the corresponding product **3m** in 83% yield. The reaction of benzylic alcohol tethered with electron-withdrawing groups gave the desired products in lesser yields, comparatively. Interestingly, 2,4-dichloro-substituted benzyl alcohol furnished the *N*-alkylated amine **3p** and **3r** in 65% and 70%, yields, respectively. Notably, no cleavage of halogen atom was observed when halide-substituted alcohols or aniline were employed.[11b] Furthermore, the reaction of 4-cyano benzyl alcohol gave the desired product **3y** in less yield (59%) along with the formation of hydrolysed product (4-cyano to amide, 22% yield) due to the presence of potassium *tert*-butoxide in the reaction. The reaction of *n*-butanol with 4-methoxy aniline failed to give corresponding product **3s** under present reaction condition. When aliphatic amines (**3t-u**) were used as the substrates the reactions yielded inseparable mixtures.

Considering the importance of alkylation of heterocylclic amines, we further expanded the scope of this methodology

towards the alkylation of aminopyridine and pyrazolopyrimidine with alcohols under optimized reaction conditions. 2-aminopyridine successfully transformed into the intermediates of bioactive drugs chloropyramine (**5b**) and mepyramine (**5c**), extensively used in first generation antihistamine. To our delight, the pharmaceutically active pyrazolopyrimidines transformed efficiently into the desired secondary amines in 59% yield (Table 3, **5e**). Furthermore, 2-indolylmethanol with 2-aminopyridine lead to products **5f** in good yield, while the reaction of unprotected 2-indolylmethanol with 2-aminopyridine failed to give corresponding **5g** product. Moreover, 2-(benzylamino)-5,7-dihydro-6*H*-benzo[*b*]pyrimido[4,5-*d*]azepin-6-one successfully converted to corresponding alkylated product (**5h**) in 48% yield. Notably, this method is highly selective for *N*-monoalkylated products and no dialkylation of amines was observed. Application of this methodology with anilines having amide, carbonyl, ester functionalities, and secondary benzylic alcohols was not successful (see Table S5 in the Supporting Information).

To demonstrate the practicality of this SmI_2-Catalyzed reaction, we carried out gram-scale synthesis of products **5b** under the optimal reaction. The reaction proceeded smoothly and afforded the desired products **5b** in 71% yield, suggesting that the large-scale synthesis of monoalkylation of amines might be possible (see scheme S5 in the Supporting Information for detail).

Table2: Alkylation of aniline derivatives with various primary alcohols[a,b]



[a]Reaction conditions: 1.0 mmol aniline, 1.5 mmol benzyl alcohol, 1.0 mmol Base, 3 mL solvent.[b] Reaction yields. Reaction was performed in microwave at 140 °C for 1 h.[c]Reaction was carried out with 1.5 mmol of aliphatic alcohol. [d]Reaction was carried out with 1.0 mmol of aliphatic amines.

To establish the synthetic utility of present protocol, we performed an intramolecular cyclization of 1,2-phenylenediamine with benzyl alcohol. Fascinatingly, the reaction proceeded smoothly to afford benzimidazole in 52% yield (Scheme 2).

Scheme 2. Direct Synthesis of Benzimidazole

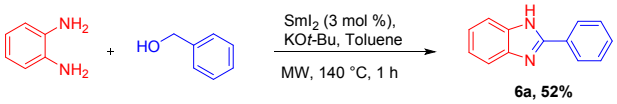
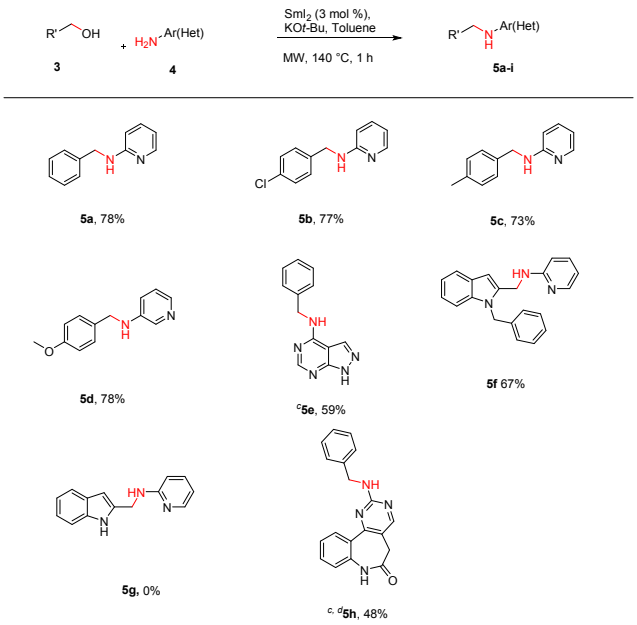
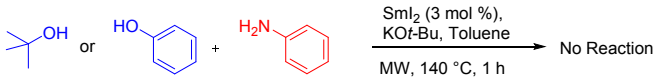


Table3: Alkylation of heteroaromatic amines with various primary alcohols[a,b]



[a]Reaction conditions: 1.0 mmol aniline, 1.5 mmol benzyl alcohol, 1.0 mmol Base, 3 mL solvent. [b]Reaction yields. [c]Reaction at 140 °C for 1.5 h. [d]Dioxane used as a solvent.

Scheme 3. Reaction of *tert*-Butyl Alcohol or Phenol with Aniline

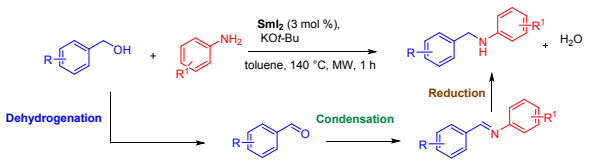


To gain insight into the reaction mechanism, the reactions of *tert*-butanol and phenol were studied with aniline under the optimized reaction conditions. No products were formed, which suggests the pathway involves initial alcohol

dehydrogenation, condensation and the imine reduction (Scheme 3).[19a]

Further, we studied the reaction of 4-OMe benzyl alcohol with 3-amino pyridine in presence of SmI_2 catalyst and KO*t*-Bu (Scheme S1). 4-anisaldehyde was found to be formed after 10 min (detected by NMR) which further reacted with 3-amino pyridine to give the desired products (Scheme S2). Based on the above experiment and control experiments (scheme S4), we propose the plausible reaction pathway as depicted in Scheme 4. In the presence of SmI_2 catalyst and KO*t*-Bu, dehydrogenation of primary alcohol gives the corresponding aldehyde, which subsequently reacts with the amine to form the imine intermediate. Further, SmI_2 catalyzed reduction of the imine intermediate gives the desired amine product. With the observations made and literature precedence[19], we propose that the active species of Sm to be Sm (III). The formation of Sm (III)-H is reported.[19e] Further, microwave reaction conditions might be favouring hydrogenation due to the high pressure created in the vial, promoting partially a better redistribution of H_2 which can be seen from table 1, entries 1-3. The stepwise details for this *N*-alkylation protocol still remain an area for further experimental and computational investigations. Further extensions and deeper mechanistic insights of the reactions are in progress.

Scheme 4. Plausible reaction mechanism for SmI_2-Catalyzed *N*-monoalkylation of amines



In summary, we have reported the first example of SmI_2 catalyzed selective and direct *N*-alkylation of amines with alcohols. The reaction tolerates a wide range of functional groups and allows the synthesis of alkylated heterocyclic amines. The developed protocol provides an interesting strategy for sustainable C-N bond synthesis.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO–d_6 on a 500 MHz and 125 MHz spectrometer respectively, using tetramethylsilane as the internal standard. Spin multiplicities were described as s (singlet), d (doublet), dd (double douplet), t (triplet), and m (multiplet). Coupling constant (*J*) values were expressed in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on ESI-QTOF mass spectrometer. All the melting points were recorded on micromelting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on MERCK precoated silica gel $60_{F\text{-}254}$ (0.5 mm) aluminum plates. TLC spot visualization was achieved under UV light. Column chromatography was performed using silica gel 100-200.
Microwave reactor (make-Anton Paar GmbH).

Microwave Irradiation Experiments. Microwave irradiation experiments were conducted in a Monowave 300 single-mode microwave reactor.[20] SiC10 Silicon Carbide reaction vessels (10 mL) or reusable Pyrex vials (30 mL) are utilized for conducting the reactions.

General procedure for alkylation of amines. Amines (1.0 mmol), alcohols (1.5 mmol), KO*t*-Bu (1.0 mmol, 110 mg) and SmI_2 0.1 M solution in THF (3 mol %, 0.3 mL in inert condition) were added in a 10 mL monowave vial (SiC10) followed by toluene (2 mL). The vessel was subsequently placed in the microwave cavity and irradiated for 1 h at 140 °C. The reaction mixture was cooled to room temperature and 5.0 mL of ethyl acetate was added and concentrated in vacuo. The residue was purified by column chromatography using a gradient pentane/ Et_2O (eluent system) to afford the pure products.

***N*-benzylaniline (3a):** Yield: 81% (148 mg); colourless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 7.27– 7.22 (m, 1H), 7.14 (t, *J* = 6.8 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 2H), 4.27 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 148.2, 139.6, 129.4, 128.7, 127.6, 127.3, 117.7, 113.0, 48.4; HRMS (ESI): calcd for $C_{13}H_{14}N$ $[M + H]^+$ 184.1126, found: 184.1117.

***N*-benzyl-4-bromoaniline (3b):** Yield: 82% (214 mg); colourless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 4H), 7.30 – 7.26 (m, 1H), 7.26 – 7.22 (m, 2H), 6.54 – 6.48 (m, 2H), 4.29 (brs, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.8, 138.7, 132.0, 129.3, 128.7, 127.5, 114.6, 109.4, 48.4; HRMS (ESI): calcd for $C_{13}H_{13}BrN$ $[M + H]^+$ 262.0231, found: 262.0230.

***N*-benzyl-3-chloroaniline (3c):** Yield: 77% (164 mg); colourless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (brs, 4H), 7.31 – 7.25 (m, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.69 – 6.65 (m, 1H), 6.61 (t, *J* = 2.1 Hz, 1H), 6.50 – 6.46 (m, 1H), 4.29 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 148.3, 138.1, 135.1, 130.3, 128.8, 127.7, 127.6, 118.3, 113.4, 111.9, 48.7; HRMS (ESI): calcd for $C_{13}H_{13}ClN$ $[M + H]^+$ 218.0737, found: 218.0729.

***N*-benzyl-4-methoxyaniline (3d):** Yield: 80% (170 mg); colourless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H), 7.34 – 7.30 (m, 2H), 7.28 – 7.24 (m, 1H), 6.80 – 6.75 (m, 2H), 6.71 – 6.64 (m, 2H), 4.28 (s, 2H), 3.73 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.1, 140.7, 138.5, 128.6, 128.0, 127.4, 115.4, 114.9, 55.8, 50.1; HRMS (ESI): calcd for $C_{14}H_{16}NO$ $[M + H]^+$ 214.1232, found: 214.1226.

***N*-benzyl-4-(*tert*-butyl)aniline (3e):** Yield: 82% (196 mg); brown solid; m.p. 49–50 °C; ^1H NMR (500 MHz, $CDCl_3$) 7.38 (dd, *J* = 7.9, 1.0 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 7.23 – 7.20 (m, 2H), 6.69 – 6.65 (m, 2H), 4.30 (s, 2H), 1.27 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.5, 141.6, 138.8, 128.6, 127.9, 127.4, 126.1, 113.6, 49.4, 33.9, 31.5; HRMS (ESI): calcd for $C_{17}H_{22}N$ $[M + H]^+$ 240.1752, found: 240.1739.

***N*-benzyl-4-fluoroaniline (3f):** Yield: 68% (135 mg); colourless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 4H), 7.22 – 7.17 (m, 1H), 6.83 – 6.76 (m, 2H), 6.53 – 6.45 (m, 2H), 4.20 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.1 (d, $J_{C\text{-}F}$ = 235.5 Hz), 143.1, 138.0, 127.6, 126.6, 126.3, 114.7, 114.6, 113.0, 112.9, 48.1; HRMS (ESI): calcd for $C_{13}H_{13}FN$ $[M + H]^+$ 202.1032, found: 202.1027.

***N*-benzyl-4-chloroaniline (3g):** Yield: 76% (161 mg); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 7.13 – 7.04 (m, 2H), 6.57 – 6.46 (m, 2H), 4.28 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.6, 139.0, 129.1, 128.7, 127.5, 127.4, 122.2, 114.1, 48.4; HRMS (ESI): calcd for $C_{13}H_{13}ClN$ $[M + H]^+$ 218.0737, found: 218.0727.

***N*-benzyl-3-phenoxyaniline (3h):** Yield: 81% (222 mg); brown solid; m.p. 56–57 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 7H), 7.11 – 7.04 (m, 2H), 7.01 – 6.97 (m, 2H), 6.40 – 6.36 (m, 1H), 6.36 – 6.32 (m, 1H), 6.30 (t, J = 2.2 Hz, 1H), 4.27 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.5, 157.2, 149.5, 139.0, 130.3, 129.6, 128.7, 127.6, 127.4, 123.1, 119.0, 108.2, 108.0, 103.5, 48.4; HRMS (ESI): calcd for $C_{19}H_{18}NO$ $[M + H]^+$ 276.1388, found: 276.1364.

2,5-dimethyl-*N*-(4-methylbenzyl)aniline (3i): Yield: 78% (174 mg); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 7.8 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 6.94 (d, J = 7.3 Hz, 1H), 6.50 (d, J = 8.8 Hz, 2H), 4.29 (s, 2H), 2.33 (s, 3H), 2.26 (s, 3H), 2.10 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 145.7, 136.9, 136.8, 129.9, 129.3, 127.8, 119.2, 118.1, 111.3, 48.4, 21.5, 21.1, 17.1; HRMS (ESI): calcd for $C_{16}H_{20}N$ $[M + H]^+$ 226.1596, found: 226.1591.

***N*-(4-methylbenzyl)aniline (3j):** Yield: 80% (157 mg); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 7.20 – 7.12 (m, 4H), 6.75 – 6.70 (m, 1H), 6.65 (dd, J = 8.6, 0.9 Hz, 2H), 4.28 (s, 2H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.8, 137.0, 136.0, 129.3, 129.3, 127.6, 117.9, 113.2, 48.4, 21.1; HRMS (ESI): calcd for $C_{14}H_{16}N$ $[M + H]^+$ 198.1283, found: 198.1277.

4-fluoro-*N*-(4-methylbenzyl)aniline (3k): Yield: 78% (167 mg); brown solid; m.p. 73–74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.90 – 6.81 (m, 2H), 6.60 – 6.51 (m, 2H), 4.22 (s, 2H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (125MHz, $CDCl_3$) δ 156.1 (d, $J_{C\text{-}F}$ = 235.5 Hz), 155.2, 144.0, 137.1, 135.8, 129.3, 127.6, 115.8, 115.6, 114.2, 114.1, 49.0, 21.1; HRMS (ESI): calcd for $C_{14}H_{15}FN$ $[M + H]^+$216.1189, found: 216.1183.

4-bromo-*N*-(4-methylbenzyl)aniline (3l): Yield: 77% (210 mg); colourless solid; m.p. 78-79; ^{1}H NMR (500 MHz, $CDCl_3$) 7.24 – 7.19 (m, 4H), 7.15 (d, J = 7.9 Hz, 2H), 6.54 – 6.43 (m, 2H), 4.23 (s, 2H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.0, 137.1, 135.7, 132.0, 129.4, 127.5, 114.6, 109.2, 48.1, 21.1; $C_{14}H_{15}BrN$ $[M + H]^+$ 276.0388, found: 276.0383.

***N*-(4-methoxybenzyl)aniline (3m):** Yield: 83% (176 mg); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.20 (m, 2H), 7.14 – 7.08 (m, 2H), 6.82 – 6.77 (m, 2H), 6.70 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 7.7 Hz, 2H), 4.26 (s, 2H), 3.79 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.0, 145.8, 129.4, 128.3, 128.1, 117.6, 113.0, 112.9, 54.3, 47.5; HRMS (ESI): calcd for $C_{14}H_{16}NO$ $[M + H]^+$ 214.1232, found: 214.1229.

4-chloro-*N*-(4-methylbenzyl)aniline (3n): Yield: 72% (163 mg); brown solid; m.p. 68–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 2H), 7.14 (d, J = 7.9 Hz, 2H), 7.12 – 7.07 (m, 2H), 6.57 – 6.52 (m, 2H), 4.24 (s, 2H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.5, 137.1, 135.7, 129.4, 129.1, 127.5, 122.4, 114.2, 48.3, 21.1; HRMS (ESI): calcd for $C_{14}H_{15}ClN$ $[M + H]^+$ 232.0893, found: 232.0872.

***N*-(4-methylbenzyl)-3-phenoxyaniline (3o):** Yield: 78% (225 mg); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.20 (m, 2H), 7.15 – 7.05 (m, 4H), 7.03 – 6.97 (m, 2H), 6.43 – 6.39 (m, 1H), 6.36 (dd, J = 8.1, 1.6 Hz, 1H), 6.34 – 6.31 (m, 1H), 4.23 (s, 2H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.4, 157.2, 149.1, 137.1, 135.6, 130.2, 129.6, 129.3, 127.7, 123.0, 119.0, 108.5, 108.3, 103.8, 48.4, 21.1; HRMS (ESI): calcd for $C_{20}H_{20}NO$ $[M + H]^+$ 290.1545, found: 290.1540.

4-chloro-*N*-(2,4-dichlorobenzyl)aniline (3p) Yield: 65% (182 mg); brown solid; m.p. 71–72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 7.32 – 7.27 (m, 3H), 7.13 – 7.07 (m, 2H), 6.56 – 6.50 (m, 1H), 4.28 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.0, 137.2, 133.2, 129.1, 128.8, 128.7, 122.8, 114.3, 47.9; HRMS (ESI): calcd for $C_{13}H_{11}Cl_3N$ $[M + H]^+$ 285.9957, found: 285.9946.

4-chloro-*N*-(4-methoxybenzyl)aniline (3q): Yield: 77% (190 mg); brown solid; m.p. 77–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 7.14 – 7.06 (m, 2H), 6.90 – 6.84 (m, 2H), 6.59 – 6.51 (m, 2H), 4.21 (s, 2H), 3.79 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.0, 146.4, 130.7, 129.1, 128.8, 122.4, 114.2, 114.1, 55.3, 48.1; HRMS (ESI): calcd for $C_{14}H_{15}ClNO$ $[M + H]^+$ 248.0842, found: 248.0836.

***N*-(2,4-dichlorobenzyl)aniline (3r):** Yield: 70% (175 mg); brown solid; m.p. 63–64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (brs, 3H), 7.11 – 7.03 (m, 2H), 6.68 – 6.61 (m, 1H), 6.54 – 6.49 (m, 2H), 4.20 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.7, 138.0, 132.9, 129.3, 128.8, 118.0, 113.1, 47.7; HRMS (ESI): calcd for $C_{13}H_{12}Cl_2N$ $[M + H]^+$ 252.0347, found 252.0314.

***N*-((1-benzyl-1*H*-indol-2-yl)methyl)aniline (3v):** Yield: 73% (226 mg); brown solid; m.p. 162–163; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.48 – 7.45 (m, 1H), 7.36 – 7.29 (m, 1H), 7.27 – 7.22 (m, 2H), 7.21 – 7.17 (m, 1H), 7.04 – 6.95 (m, 5H), 6.57 (dd, J = 8.6, 0.9 Hz, 2H), 6.52 – 6.48 (m, 1H), 6.45 (s, 1H), 6.07 (t, J = 5.7 Hz, 1H), 5.48 (s, 2H), 4.32 (d, J = 5.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 148.9, 139.0, 138.9, 137.8, 129.2, 129.0, 127.8, 127.6, 126.7, 121.4, 120.3, 119.7, 116.6, 112.9, 110.2, 101.3, 46.5, 40.3; HRMS (ESI): calcd for $C_{22}H_{21}N_2$ $[M + H]^+$ 313.1705, found: 313.1697.

***N*-benzyl-3-nitroaniline (3w):** Yield: 69% (158 mg); Orange solid; m.p. 102–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.0, 1.7 Hz, 1H), 7.48 (t, J = 2.2 Hz, 1H), 7.36 (brs, 4H), 7.32 – 7.27 (m, 2H), 6.92 (dd, J = 8.1, 2.0 Hz, 1H), 4.39 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 149.4, 148.2, 137.7, 129.8, 128.9, 127.8, 127.6, 119.2, 112.6, 107.1, 48.4; HRMS (ESI): calcd for $C_{13}H_{13}N_2O_2$ $[M + H]^+$ 229.0977, found: 229.0967.

***N*-benzyl-3-(trifluoromethyl)aniline (3x):** Yield: 72% (180 mg); colourless oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.39 – 7.31 (m, 4H), 7.27 – 7.22 (m, 2H), 6.86 (brs, 1H), 6.84 – 6.78 (m, 2H), 4.32 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 149.5, 139.9, 130.3 (q, $J_{C\text{-}F}$ = 31.3 Hz), 129.5 (q, $J_{C\text{-}F}$ = 293.7 Hz), 128.8, 127.7, 127.3, 126.1, 123.9, 116.0, 112.1 (q, $J_{C\text{-}F}$ = 3.8 Hz), 108.6 (q, $J_{C\text{-}F}$ = 3.6 Hz), 46.7; HRMS (ESI): calcd for $C_{14}H_{13}F_3N$ $[M + H]^+$ 252.1000, found: 252.0996.

4-((phenylamino)methyl)benzonitrile (3y): Yield: 59 % (123 mg); brown solid; m.p. 87–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.59 (m, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.21 – 7.08 (m, 2H), 6.77 – 6.73 (m, 1H), 6.60 – 6.57 (m, 2H), 4.42 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.2, 145.2, 132.5, 129.4,

127.8, 118.9, 118.4, 113.2, 111.0, 48.0; HRMS (ESI): calcd for $C_{14}H_{13}N_2$ $[M + H]^+$ 209.1079, found: 209.1072.

***N*-(2-nitrobenzyl)aniline (3z):** Yield: 61% (139 mg); Orange oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.58 – 7.53 (m, 1H),), 7.43 – 7.38 (m, 1H), 7.19 – 7.11 (m, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.59 (dd, *J* = 8.6, 1.0 Hz, 2H), 4.72 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 148.3, 147.1, 135.4, 133. 7, 129.9, 129.4, 128.0, 125.2, 118.3, 113.2, 45.9; HRMS (ESI): calcd for$C_{13}H_{13}N_2O_2$ $[M + H]^+$ 229.0977, found: 229.0963.

***N*-benzylpyridin-2-amine (5a):** Yield: 78% (142 mg); colourless solid; m.p. 92–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (brs, 1H), 7.42 – 7.31 (m, 5H), 7.29 – 7.24 (m, 1H), 6.61 – 6.56 (m, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 4.99 (brs, 1H), 4.50 (d, *J* = 5.8 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.6, 148.1, 139.1, 137.6, 128.7, 127.4, 127.3, 113.2, 106.8, 46.3; HRMS (ESI): calcd for $C_{12}H_{13}N_2$ $[M + H]^+$ 185.1079, found: 185.1078.

***N*-(4-chlorobenzyl)pyridin-2-amine (5b):** Yield: 77% (166 mg); colorless solid; m.p. 90–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.7 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.29 (brs, 4H), 6.62 (t, *J* = 4.7 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 5.27 (brs, 1H), 4.49 (d, *J* = 5.7 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.7, 146.2, 138.6, 137.2, 133.1, 128.8, 128.6, 113.2, 107.4, 45.6; HRMS (ESI): calcd for $C_{12}H_{12}ClN_2$ $[M + H]^+$ 219.0689, found: 219.0684.

***N*-(4-chlorobenzyl)pyridin-2-amine (5c):** Yield: 73% (145 mg); white solid; m.p. 73–74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.3 Hz, 1H), 7.47 – 7.35 (m, 1H), 7.24 (s, 1H), 7.19 – 7.11 (m, 2H), 6.67 – 6.53 (m, 1H), 6.39 (d, *J* = 8.4 Hz, 3H), 5.14 (brs, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.4, 147.3, 137.9, 137.0, 135.8, 129.3, 127.3, 113.0, 107.0, 46.1, 21.1; HRMS (ESI): calcd for $C_{13}H_{15}N_2$ $[M + H]^+$ 199.1235, found: 199.1228.

***N*-(4-methoxybenzyl)pyridin-3-amine (5d):** Yield: 78% (165 mg); colourless solid; m.p. 142–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.6 Hz, 1H), 7.96 (d, *J* = 3.7 Hz, 1H), 7.31 – 7.23 (m, 4H), 7.06 (dd, *J* = 8.2, 4.6 Hz, 1H), 6.94 – 6.85 (m, 3H), 4.26 (s, 2H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.1, 144.1, 138.9, 136.2, 130.5, 128.8, 123.7, 118.6, 114.2, 55.3, 47.4; HRMS (ESI): calcd for $C_{13}H_{15}N_2O$ $[M + H]^+$ 215.1184, found: 215.1183.

***N*-benzyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5e):** Yield: 59% (132 mg); brown solid; m.p. 265–266 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.42 (brs, 1H), 8.69 (s, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.39 – 7.31 (m, 4H), 7.29 – 7.22 (m, 1H), 4.75 (d, *J* = 5.9 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 156.7, 156.1, 154.9, 139.8, 132.8, 128.8, 127.9, 127.4, 100.4, 43.6; HRMS (ESI): calcd for $C_{12}H_{15}N_5$ $[M + H]^+$ 226.1093, found: 226.1086.

***N*-((1-benzyl-1*H*-indol-2-yl)methyl)pyridin-2-amine (5f):** Yield: 67% (210 mg); brown solid; m.p. 196–197; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 – 7.94 (m, 1H), 7.54 – 7.47 (m, 1H), 7.39 – 7.33 (m, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.20 (m, 1H), 7.07 – 7.01 (m, 3H), 7.00 – 6.96 (m, 1H), 6.54 – 6.48 (m, 1H), 6.46 (s, 2H), 5.49 (s, 2H), 4.63 (d, *J* = 5.6 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 158.8, 147.8, 139.5, 138.8, 137.6, 137.1, 129.0, 127.8, 127.5, 126.7, 121.4, 120.3, 119.7, 112.5, 110.3, 108.9, 101.1, 46.5, 37.6; HRMS (ESI): calcd for $C_{21}H_{20}N_3$ $[M + H]^+$ 314.1657, found: 314.1645.

2-(benzylamino)-5,7-dihydro-6*H*-benzo[*b*]pyrimido[4,5-*d*]azepin-6-one (5h): Yield: 48% (150 mg); brown solid; m.p. 231–232; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.14 (brs, 1H), 8.29 (brs, 1H), 8.02 – 7.77 (m, 2H), 7.60 – 7.10 (m, 7H), 4.56 (brs, 2H), 3.26 (brs, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 172.3, 162.4, 157.9, 141.0, 138.4, 131.4, 130.3, 129.6, 128.6, 127.6, 127.0, 124.2, 122.4, 115.9, 44.7, 36.6; HRMS (ESI): calcd for $C_{19}H_{17}N_4O$ $[M + H]^+$ 317.1402, found: 317.1417.

2-phenyl-1*H*-benzo[*d*]imidazole (6a): Yield: 52% (100 mg); brown solid; m.p. 291–292 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.21 (d, *J* = 7.4 Hz, 2H), 7.69 (d, *J* = 6.3 Hz, 1H), 7.59 –7.54 (m, 3H), 7.52 – 7.47 (m, 1H), 7.22 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO) δ 151.7, 144.3, 135.5, 130.7, 130.3, 129.4, 126.9, 123.0, 122.1, 119.3, 111.8; HRMS (ESI): calcd for $C_{13}H_{11}N_2$ $[M + H]^+$ 195.0922, found: 195.0921.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful to DoP, Ministry of Chemicals & Fertilizers, Govt. of India, New Delhi, for the award of NIPER fellowship.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for the products (PDF).

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