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Preyssler catalyst-promoted rapid, clean, and efficient condensation reactions for 3*H*-1,5-benzodiazepine synthesis in solvent-free conditions

Gustavo A. Pasquale [a,b], Diego M. Ruiz [a], Jorge L. Jios [c], Juan C. Autino [a], Gustavo P. Romanelli [a,b,*]

[a] Centro de Investigación y Desarrollo en Ciencias Aplicadas 'Dr. Jorge J. Ronco' (CINDECA-CCT-CONICET), Universidad Nacional de La Plata, Calle 47 N° 257, B1900AJK La Plata, Argentina
[b] Cátedra de Química Orgánica, Facultad de Ciencias Agrarias y Forestales, Universidad Nacional de La Plata/CISaV, Calles 60 y 119 s/n, B1904AAN La Plata, Argentina
[c] Unidad Laseisic-Plapimu (UNLP-CIC), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, 47 esq. 115, (1900) La Plata, Argentina

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ABSTRACT

A simple, convenient, and environmentally benign synthesis of 1,5-benzodiazepines is developed by condensing different *o*-phenylenediamines and 1,3-aryl-1,3-propanodiones. The reaction is catalyzed by a Preyssler ($NaH_{14}P_5W_{30}O_{110}$, HPA) heteropolyacid as a safe, clean, and recyclable catalyst. The method is operationally simple and provides access to a variety of 1,5-benzodiazepines in good to excellent yields.

Benzodiazepines are privileged heterocyclic ring systems due to their broad and important biological properties.[1] Some functionalized benzodiazepines have pharmacological properties such as anti-inflammatory, analgesic, antiallergenic antiulcerative, antihistaminic, antipyretic, sedative, antidepressant, hypnotic, bactericide, and fungicide[2] properties, among others. Other benzodiazepines have also been used in crop control such as pesticides, antifeedants for insect control, herbicides, and fungicides.[3] Their synthesis has received special attention in the field of medicinal chemistry because the use of 1*H*-1,5-benzodiazepines has been extended to treat various diseases such as cancer, viral infection, and cardiovascular disorders.[2a]

3*H*-1,5-Benzodiazepines are principally synthesized by condensation of *o*-phenylenediamines with 1,3-dicarbonyl compounds and β-halo-ketones, in general in the presence of an acid catalyst.[4] Different reagents have been reported in the literature for the synthesis of 1,5-benzodiazepines including: concd-HCl, SiO_2, or polyphosphoric acid (PPA),[5] BF3-OEt,[6] $Yb(OTf)_3$,[7] $Ga(OTf)_3$,[8] $NaBH_4$,[9] $MgO/POCl_3$,[10] $AgNO_3$,[11] molecular iodine,[12] CH3COOH using microwave,[13] and ionic liquid.[14] Recently, the synthesis of benzodiazepines using different solid acid catalysts such as sulfated zirconia,[15] Al_2O_3/P_2O_5,[16] PVP-$FeCl_3$,[17] zeolite,[18] bentonite,[19] and heteropolyacid catalysts using THF or acetonitrile as reaction solvent[20] has also been reported.

On the other hand, chemistry properly applied to chemical processes can also be viewed as a series of reductions in waste, energy, and auxiliary substances, leading always to the simplification of the processes in terms of the number of chemicals and steps involved.[21] Due to the growing concern for the adverse influence of organic solvents on the environment, solvent-free organic reactions have attracted the attention of organic chemists.[22] A solvent-free reaction obviously reduces pollution and brings down handling costs due to simplification of the experimental and workup procedure and saving in labor.[23]

Heteropolyacids are molecular arrangements with remarkable and diverse electronic and molecular structures that give them various applications in different areas such as medicine, material sciences, and catalysis. Among the various possible HPA structures, the Keggin-type primary structure deserves to be mentioned, due to its widely reported applications.[24] As part of a research project to develop environmentally friendly organic reactions, we used bulk or silica-supported heteropolyacids with Preyssler structure as recyclable catalyst in the solvent-free synthesis of flavones,[25] *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines,[26] phenyl cinnamates,[27] and 1,1-diacetates[28] to name some examples.

According to our interest in the green protocols in organic synthesis, here we describe the use of a Preyssler heteropolyacid as a

* Corresponding author. Tel.: +54 221 423 6758x438; fax: +54 221 425 2346.
E-mail address: gpr@quimica.unlp.edu.ar (G.P. Romanelli).

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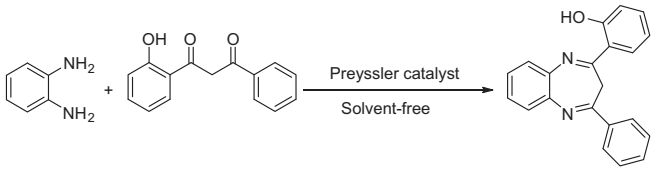
Table 1
$NaH_{14}P_5W_{30}O_{110}$-catalyzed reactions of *o*-phenylenediamine and 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione

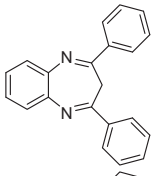
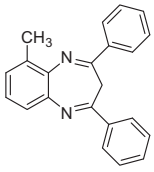
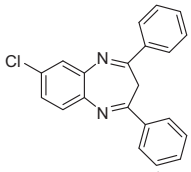
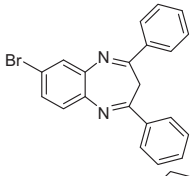
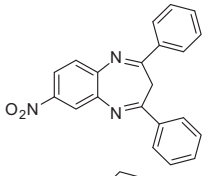
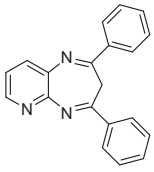


1 **2** **3 g**

Entry	HPA (mol %)	Molar ratio 1:2	Temperature (°C)	Time (min)	**3g** Yield[a] (%)
1	–	2:1	130	30	5
2	1	2:1	130	15	93
3	0.5	2.1	130	15	53
4	1	1:1	130	15	76
5	1	2:1	110	15	49
6	1	2.1	80	15	–
7	1	2.1	140	15	88
8	1	2.1	130	30	92
9	1	2.1	110	30	–

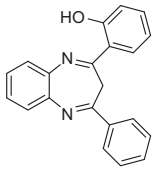
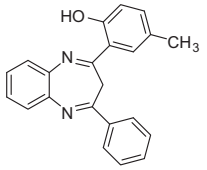
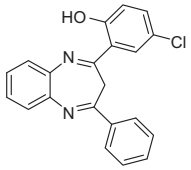
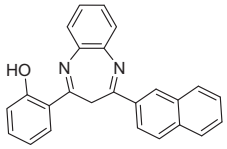
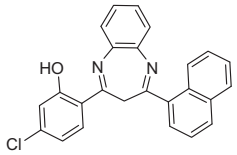
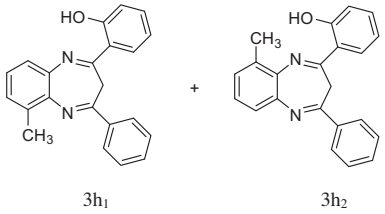
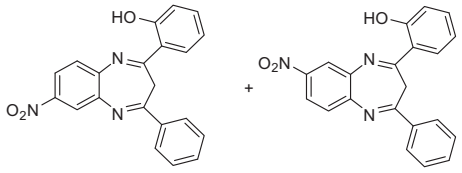
[a] Isolated yield after flash chromatography.

Table 2
1,5-Benzodiazepines from *o*-phenylenediamines and 1,3-diaryl-1,3-propanediones

Compounds	Product	Yield[a] (%)	Mp (°C)
3a		53	137–138 Lit. 138–140[29]
3b		95	98–100 New compound
3c		84	160–162 Lit. no data[30]
3d		76	170–172 Lit. no data
3e		–	–
3f		–	–

(*continued on next page*)

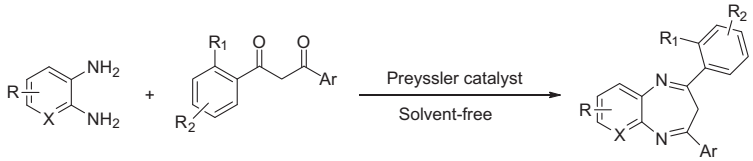
Table 2 (*continued*)

Compounds	Product	Yield[a] (%)	Mp (°C)
3g		93	180–181 Lit. 183–184[31]
3h		70	187–188 Lit. 187–188[31]
3i		75	183–184 186–187[31]
3f		59	187–188 °C New compound
3g		80	191–193 °C New compound
3h	 $3h_1$ $3h_2$	58 Regioisomermixture 1:2	3h1 141–143 3h2 152–153 New compounds
3i		–	–

[a] Isolated yield after flash chromatography.

solid and reusable catalyst, in the solvent-free synthesis of 1*H*-1, 5-benzodiazepines, by condensation reaction of *o*-phenylenediamines with several 1,3-diaryl-1,3-propanediones (Scheme 1).

First, we prepare the HPA catalyst, and then we study its catalytic activity in the mentioned reaction. The Preyssler heteropolyanion was prepared from $Na_2WO_4.2H_2O$ and H_3PO_4 according to



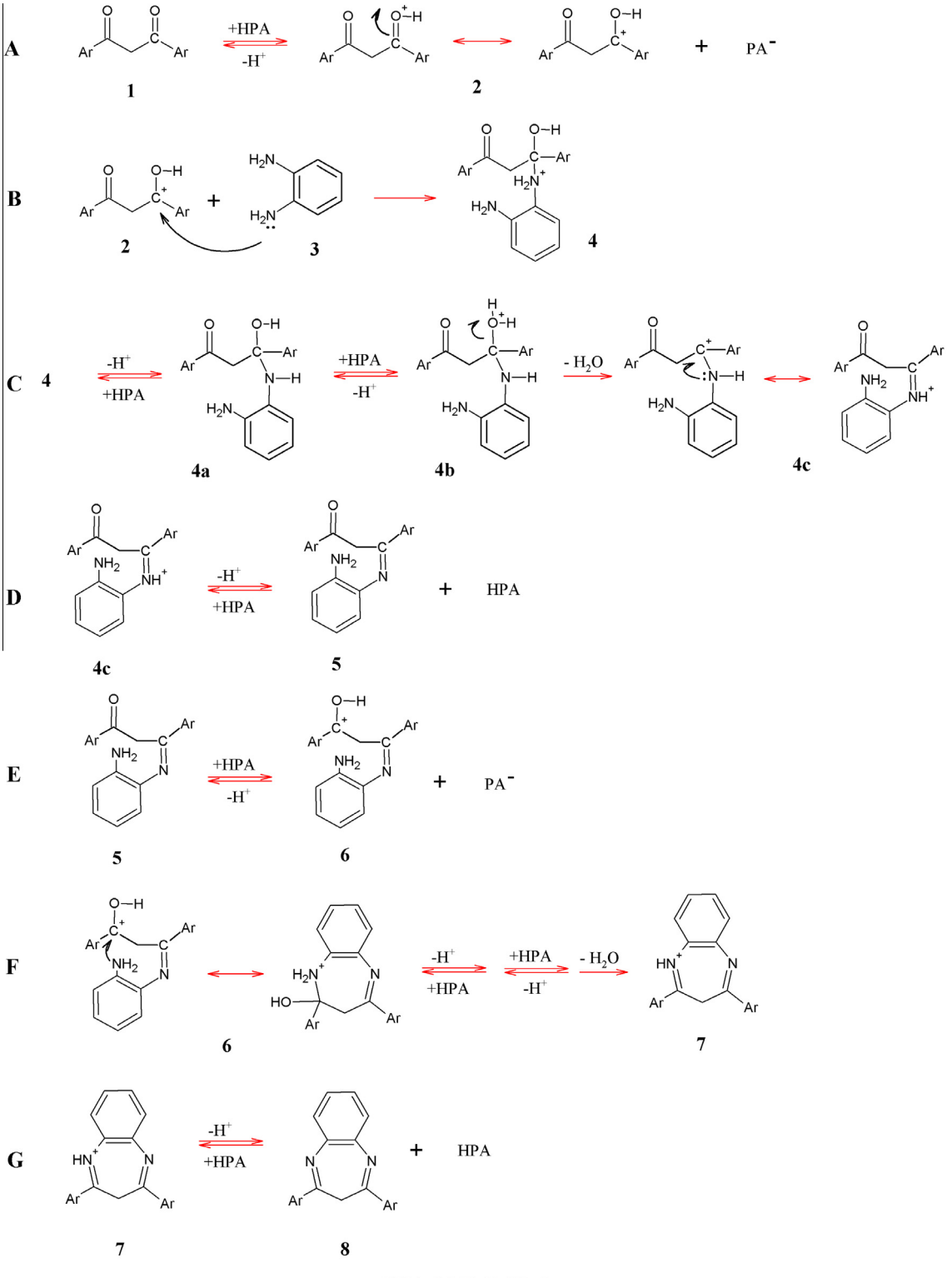
R = H, 2-CH_3 ,3-Cl, 3-Br, 3-NO_2
R_1 = H, OH
R_2 = H, 4-Cl, 5-Cl, 4-CH_3
Ar = aryl, 1-naphtyl, 2-naphtyl
X = CH, N

Scheme 1. General scheme of reaction.

Table 3
Recyclability of the HPA in the synthesis of **3f** over 5 runs

Entry	Cycle	Yield **3f** (%)
1	Use	93
2	1st reuse	90
3	2nd reuse	89
4	3rd reuse	89
5	4th reuse	88

the previously reported method, and converted to the corresponding acid $H_{14}[NaP_5W_{30}O_{110}]$ by passing it through a Dowex-50-X8 ion-exchange column.[27] The HPA catalyst was characterized by ^{31}P MAS-NMR and FT-IR spectroscopy.[32] The ^{31}P NMR-MAS spectra show five peaks at −10.2, −10.6, −12.8, −13.5, and −13.8 ppm. Meanwhile, the FTIR spectrum also shows characteristic bands of the Preyssler anion at 1641, 1164, 1087, 958, 916, and 798 cm^{-1}, respectively.[27] In a previous work, we reported a study about the



Scheme 2. Suggested mechanism for the formation of 1,5-benzodiazepines catalyzed by a Preyssler catalyst.

acidic characteristic of this catalyst using potentiometric tritration.[27] The maximum acid strength of the acid sites (*E*) for the catalyst is 862 mV. This *E* value indicates very Brönsted strong acid sites for the catalyst, and it was similar to the obtained for bulk commercial Keggin HPA.

The optimal reaction conditions were examined employing 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanodione (1 mmol), and 1,2-phenylenediamine as substrates.[33] Several reaction conditions were checked: temperature, reaction time, amount of catalyst, and molar ratio of substrates (Table 1). When a mixture of both substrates and the catalyst (1 mmol % of active phase) was stirred at 130 °C under solvent-free conditions, the corresponding 3*H*-1,5-benzodiazepine (Table 1, entry 2) was formed as the only reaction product with a 93% yield and in a short reaction time (15 min). Under the same reaction conditions and in the absence of the catalyst, the corresponding 1*H*-1,5-benzodiazepine was obtained only with 5% yield (Table 1, entry 2). In this test several unidentified side products were detected by TLC. In these equilibrium reactions, the excess of one of the reactants improves yields. Although yields are good when reactants react in an equimolar ratio (76%, Table 1, entry 4), rising to 93% when using a 100% excess of the diamine substrate (Table 1, entry 2).

Encouraged by the remarkable results obtained with the above reaction and in order to show the generality and scope of this catalytic method, the 1*H*-1,5-benzodiazepine synthesis from a series of 1,2-phenylenediamines and 1,3-diaryl-1,3-propanediones was studied under similar reaction conditions. The results are summarized in Table 2. In most of the studied cases, the reaction proceeded smoothly. 1,2-Phenylenediamines having either weak electron-withdrawing or electron-releasing substituents, including 2-methyl, 3-chloro, and 3-bromo, reacted efficiently to give good to excellent yields of the desired 1,5 benzodiazepines (Table 2). However, strongly electron-withdrawing groups or electron-deficient aromatic rings decrease dramatically the nucleophilicity of amines and the reaction does not take place. As shown in Table 2 when 4-nitro-1,2-phenylenediamine and 2,3-diaminopyridine were used as substrate, the benzodiazepines 3e, 3f, 3i1, and 3i2 were not obtained. It is noteworthy, that when we studied the reaction between 3-methyl-1,2-phenylenediamine and 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanodione as substrate, two regioisomers were obtained as expected (58%). The regioisomers were purified by repeated flash chromatography and recrystallization to give the compounds 3h1 and 3h2 with 9% and 12% yields, respectively, after recrystallization. All products listed in Table 2 were characterized by ^{1}H NMR and ^{13}C NMR, and the corresponding melting points and elemental analysis were determined.

We also investigated the reuse of the catalyst. For this purpose after completion of the reaction, toluene (2 × 2 mL) was added to the semisolid reaction mixture.[34] The catalyst was dried under vacuum (25 °C) and reused in these conditions for a new reaction cycle. The yields of benzodiazepine **3g** for the first, second, third, and fourth reuse were 90%, 89%, 89%, and 88%, respectively (see Table 3).

A rational mechanism for the formation of compound **8** is postulated in Scheme 2 for the reaction of 1,2-phenylenediamine and 1,3-diphenyl-1,3-propanodione. The reaction is thought to take place in seven steps: (A) the activation of one of the carbonyl groups of 1,3-diphenyl-1,3-propanedione **1** with the Preyssler heteropolyacid (HPA) to give the intermediate **2**; (B) the nucleophilic attack of an amino group of the 1,2-phenylenediamine **3** to the activated carbon to give the intermediate **4**; (C) the transfer of the proton from the amino group (4) to the hydroxyl group (4a) to give the intermediate 4b through the HPA and the consecutive loss of a molecule of water with the formation of the intermediate **4c**; (D) the loss of the imino proton of the intermediate **4c** and the regeneration of the HPA and the production of the imino compound **5**; (*E*) the activation of the other carbonyl group present in **5** with the heteropolyacid (HPA) to generate—in a way analogous to the step (B)—a new intermediate **6**; (F) the intramolecular nucleophilic attack of the amino group to the activated carbonyl group giving the formation of the heterocyclic intermediate that undergoes the same proton transference as in step (C) with a loss of a second molecule of water to give intermediate **7**; and (G) the loss of a proton to give the HPA regeneration and benzodiazepine **8**.

In conclusion, a very simple and convenient catalytic method was developed for the synthesis of 1,5-benzodiazepine derivatives from a multicomponent condensation reaction, under solvent-free conditions. The procedure has the advantages of low environmental impact, high yields, high selectivity, short reaction time, and the recovery of the catalyst by simple filtration. The use of an insoluble catalyst instead of soluble inorganic acids contributes to waste reduction. Further investigations about the use of this catalyst in the more sophisticated heterocyclic synthesis and in the biomass valorization are in progress in our laboratory.

Acknowledgements

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32. *Catalyst preparation and characterization.* The catalyst was prepared by a procedure described in the literature and it was characterized by ^{31}P MAS NMR, and FT-IR XRD. The ^{31}P MAS NMR spectra were recorded in Bruker MSL-400 equipment operating at frequencies of 121.496 MHz. A sample holder of 5 mm diameter and 17 mm in height was used. The spin rate was 2.1 kHz, and several hundreds of pulse responses were collected. Chemical shifts were expressed in parts per million with respect to 85% H_3PO_4 as external standard for ^{31}P NMR. The Fourier transform infrared (FT-IR) spectra of the solids were obtained using a Bruker IFS 66 FT-IR spectrometer and pellets in KBr in the 400–4000 cm^{-1} wavenumber range. Potentiometric titration was performed using a Metrohm Titrino Basic 794, with LL Solvotrode LiCl electrode.
33. *General procedure for the synthesis of 1,5-benzodiazepines* **3**. A mixture of 1.3-diaryl-1,3-propanodione, 1,2-phenylenediamine and 1 mmol % of HPA (ca. 57 mg) was stirred and heated at 120 °C in a preheated oil bath for approx. 15 min. After completion of the reaction as indicated by TLC (ethyl acetate–hexane, 1:4), hot toluene was added (5 mL). The solvent was dried over Na_2SO_4, filtered and concentrated under reduced pressure to leave the crude product that was cleaned by short column chromatography over silica gel (mixtures of ethyl acetate–hexane). After chromatographic separation the products were purified by recrystallization from EtOH. Characterization of selected compounds: **3b** ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.60 (3H, s), 3.70 (2H, br s), 7.24–7.30 (2H, m), 7.41–7.51 (7H, m), 7.98–8.06 (4H, m); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 18.7, 35.0, 125.1, 126.5, 128.1, 128.2, 128.6, 128.7, 130.4, 130.5, 136.3, 137.4, 137.5, 139.1, 140,4, 151.8, 153.9. Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.10; H, 5.81; N, 9.00. Compound **3d** ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.70 (2H, br s), 7.42–7.50 (8H, m), 7.79 (1H, dd J = 2 Hz; 0.6 Hz), 7.97–8.00 (4H, m); ^{13}C NMR (DMSO-d_6, 100 MHz): 35.2, 118.3, 128.2, 128.2, 128.5, 128.8, 128.8, 130.3, 130.9, 131.0, 131.1, 136.9, 137.0, 139.7, 141.7, 154.5, 154.0. Anal. Calcd for $C_{21}H_{15}BrN_2$: C, 67.21; H, 4.03; N, 7.47. Found: C, 67.18; H, 4.06; N, 7.50. Compound **3i** ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.80 (2H, br s), 6.96 (1H, d J = 8), 7.29 (1H, dd J = 2; J = 9), 7.37–7.46 (2H, m), 7.51–7.58 (4H, m), 7.66 (1H, dd J = 2; J = 8), 7.76 (1H, d J = 2.5), 8.04–8.08 (2H, m), 14.45 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 33.4, 118.7, 119.9, 123.2, 126.0, 126.7, 127.8, 127.9, 128.4, 128.9, 129.1, 131.3, 133.3, 136.4, 136.9, 141.7, 154.7, 157.0, 161,0. Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; N, 8.08. Found: C, 72.71; H, 4.32; N, 8.07. Compound **3g** ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.75 (2H, br s), 6.56 (1H, dd, J = 3; J = 8 Hz), 7.00 (1H, d, J = 2 Hz), 7.06 (1H, d, J = 8 Hz), 7.43–7.70 (8H, m), 7.93–8.00 (3H, m), 14.45 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 38.7, 116.5, 118.3, 119.1, 125.0, 125.0, 126.3, 126.5, 126.6, 127.0, 127.4, 127.8, 128.8, 128.9, 129.3, 130.5, 130.9, 134.0, 135.9, 136.8, 139.0, 141.3, 156.9, 157.2, 163.1. Anal. Calcd for $C_{25}H_{17}ClN_2O$: C, 75.66; H, 4.32; N, 7.06. Found: C, 75.63; H, 4.32; N, 7.07. Compound **3h1** ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.60(3H, s), 3.70 (2H, br s), 6.86–6.90 (1H, m), 7.01 (1H, dd J = 1.5; J = 8 Hz), 7.27–7.38 (3H, m), 7.48–7.53 (4H, m), 7.80 (1H, dd J = 1.5; J =8 Hz), 8.02–8.07 (2H, m), 14.80 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.2, 33.7, 118.0, 118.4, 118.6, 126.0, 126.8, 127.1, 128.3, 128.4, 128.8, 131.0, 133.5, 134.9, 136.1, 136.8, 141.6, 155.0, 157.2, 162.6. Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.93; H, 5.55; N, 8.54. Compound **3h2** ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.58 (3H, s), 3.70 (2H, br s), 6.91–6.95 (1H, m), 7.01 (1H, dd, J = 1.5; J = 8 Hz), 7.27–7.31 (2H, m), 7.35–7.43 (2H, m), 7.47–7.50 (3H, m), 7.91 (1H, dd J = 1.5; J = 8 Hz), 8.10–8.14 (2H, m), 14.60 (1H, s), ^{13}C NMR (DMSO-d_6, 100 MHz): δ 18.6, 33.2, 117.9, 118.5, 118.5, 125.5, 125.6, 127.4, 128.3, 128.4, 128.7, 130.8, 133.5, 136.8, 136.8, 136.9, 140.1, 152.8, 158.3, 162.6. Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.92; H, 5.57; N, 8.58. (s: singlet, m: multiplet, d: doublet, t:triplet, dd: double doublet, br s: broad singlet).
34. *Catalyst reuse.* Stability tests of the catalysts were carried out by running five consecutive experiments under the same reaction conditions. After each test, the catalyst was separated from the reaction mixture by filtration, washed with toluene (2 × 2 mL), dried under vacuum, and then reused.