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Copper on iron promoted one-pot synthesis of β-aminoenones and 3,5-disubstituted pyrazoles

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ABSTRACT

The reaction of hydroximoyl chlorides with acetylenes in the presence of a copper on iron bimetallic system leads to β-aminoenones via reductive ring opening of isoxazole intermediates. The valuable β-aminoenone building blocks can be isolated or transformed into pyrazoles with the addition of hydrazine in a straightforward one-pot procedure.

1. Introduction

The application of multimetallic catalyst systems for metal-catalyzed reactions provides an attractive strategy for the construction of new chemical bonds. Bimetallic catalyst systems, such as Pd/Cu are widely used in organic synthesis.[1] More recently several efficient copper/iron-promoted synthetic transformations were reported, where the cooperation of the metals was beneficial for the reaction.[2]

Copper-catalyzed reactions of hydroximoyl chlorides and terminal acetylenes via in situ nitrile oxide generation are frequently used methods for the construction of isoxazoles.[3] These five-membered heterocycles can be used in ring transformations to prepare further heterocyclic systems.[4]

β-Aminoenones are versatile synthetic intermediates that are useful synthons in several applications[5] and used in the synthesis of heterocycles (pyrazoles, pyrroles, pyridinones, pyrimidines).[6] Although several methods exist for the synthesis of *N*-substituted β-aminoenones,[7] preparation of β-aminoenones bearing a free amino group is typically achieved through reductive ring opening of isoxazoles. The most frequently used methods for isoxazole reductive ring opening are hydrogenation using Raney nickel, palladium on charcoal or platinum catalysts,[4,8] or using molybdenum (0) or iron (0) carbonyl complexes.[9] Another way to perform the N–O cleavage is through electron transfer from reducing agents, such as SmI_2,[10] Fe(II) complexes[11] or iron dichloride.[12]

The synthesis of pyrazoles remains of great interest due to their important role in the agrochemical and pharmaceutical industries.[13] Several methods exist for the synthesis of 3,5-disubstituted pyrazoles,[14] but the most important is the cyclocondensation of hydrazine with 1,3-dielectrophilic reagents, such as 1,3-dicarbonyl compounds,[15] ynones,[16] α,β-unsaturated carbonyls bearing a leaving group at the β-carbon,[17] or related compounds.

2. Results and discussion

A copper on iron catalyst was developed in our laboratory for the efficient thiolation of aromatic halides[18] and the azide–alkyne cycloaddition.[19] We also fully characterized the Cu/Fe system regarding copper content and structure.[19] As a continuation of our work, herein we report the use of this Cu/Fe bimetallic system in the dipolar cycloaddition of nitrile oxides and alkynes to prepare isoxazoles, which can be transformed into β-aminoenones in a one-pot process via reductive N–O bond cleavage using the iron as the electron source.

We began by examining the reaction of *N*-hydroxy-benzenecarboximidoyl chloride and phenylacetylene in the presence of K_2CO_3 in DMF at 100 °C, but we found only the formation of diphenylisoxazole (Table 1, entry 1). In the absence of base, the isoxazole ring was opened to form β-aminoenone and products **3** and **4** were formed in a 74:5 ratio (Table 1, entry 2). Copper itself was not able to catalyze the cleavage of N–O bond (entry 3). Increasing the amount of iron from 10 mol % up to 110%, we obtained better

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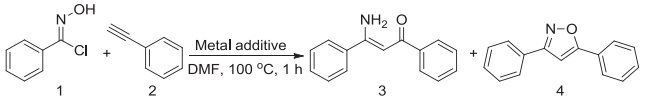
aminoenone ratios (entries 4–6), showing that a stoichiometric amount of iron is necessary to perform the reductive ring opening.

Table 1
Effect of transition metals on the cycloaddition and the reductive ring opening[a]



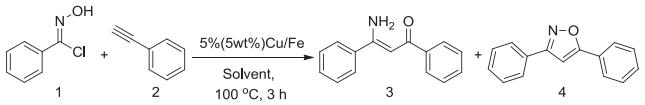
Entry	Metal	Catalyst (mol %)	Conversion[b] %	Product ratio[c] 3:4
1[d]	5 wt % Cu/Fe	5	86	0:86
2	5 wt % Cu/Fe	5	79	74:5
3	Cu powder	5	71	2:69
4	Fe powder	10	79	2:77
5	Fe powder	50	79	25:54
6[e]	Fe powder	110	82	56:26
7[f]	Cu+Fe powder	5	80	67:13
8	—	—	46	0:46

[a] Reaction conditions: 0.25 mmol *N*-hydroxy-benzenecarboximidoyl chloride, 0.25 mmol phenylacetylene, 0.1 mL DMF, 100 °C, 1 h.
[b] Based on phenylacetylene.
[c] Product ratio and conversion were determined with GC–MS.
[d] Reaction with 0.25 mmol K_2CO_3.
[e] Reaction with the same Fe content as 5 mol % (5 wt %) Cu/Fe.
[f] Reaction with the same Cu and Fe content as 5 mol % (5 wt %) Cu/Fe.

Next, we examined the synergistic effect of copper and iron in the Cu/Fe bimetallic system compared with the separate addition of copper and iron powder (entry 7). On the basis of three parallel reactions, we found similar conversions, but the reductive ring opening was faster in the presence of Cu/Fe (74:5 vs 67:13; entries 2 and 7). In the absence of any transition metal additive, the cycloaddition took place in 46% conversion after 1 h (entry 8), but the conversion reached only 498% after 20 h.

Although, DMF proved to be good solvent for the ring opening step, we examined the reaction in other media (Table 2). In water, toluene, and DMSO (entries 1–3.) the reaction gave 82, 48, and 65% conversion, respectively. However, only the cycloaddition took place and no aminoenone formation was observed. In *n*-butanol and acetonitrile (entries 4 and 5) the reductive ring opening occurred, but the conversions were found to be low relative to other solvents. DMF and DMA give similar conversions (entries 6 and 7), but interestingly in DMF the aminoenone derivative was the major product.

Table 2
Influence of solvents on the cycloaddition and the ring opening[a]

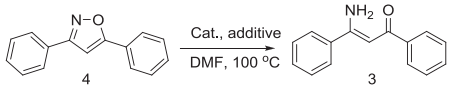


Entry	Solvent	Conversion[b] %	Product ratio[c] 3:4
1	H_2O	82	0:82
2	Toluene	48	0:48
3	DMSO	65	0:65
4	^{n}BuOH	34	10:24
5	MeCN	16	14:2
6	DMA	75	26:49
7[d]	DMF	79	74:5

[a] Reaction conditions: 0.25 mmol *N*-hydroxy-benzenecarboximidoyl chloride 0.25 mmol phenylacetylene, 0.1 mL DMF, 100 °C, 1 h.
[b] Based on phenylacetylene.
[c] Product ratio and conversion were determined with GC–MS.
[d] After 1 h.

To determine the factors responsible for the opening of the isoxazole ring, we heated 3,5-diphenylisoxazole in DMF at 100 °C under a variety of conditions (Table 3). In the absence of any metal additive, the ring opening does not occur under the reaction conditions (entry 1). Also, copper on iron itself is not able to assist the opening of the isoxazole ring (entry 2). Based upon Truscello's results,[12] we tried $FeCl_2$ and $FeCl_3$ as promoters of the ring opening step, but the formation of β-aminoenone did not occur in the presence of either additive (entries 3 and 4).

Table 3
Study of the ring opening of isoxazoles[a]



Entry	Reagent	Additive	Conversion (%)[b]	
			After 1 h	After 3 h
1	—	—	0	0
2	5% (5 wt %) Cu/Fe	—	0	0
3[c]	1.1 equiv $FeCl_2$	—	0	0
4[c]	1.1 equiv $FeCl_3$	—	0	0
5[d]	5% (5 wt %) Cu/Fe	concd HCl (aq)	30	65
6[e]	—	HCl	0	0
7[e]	5% (5 wt %) Cu/Fe	HCl	90	100
8[c,e]	1.1 equiv $FeCl_2$	HCl	0	0
9[c,e,f]	1.1 equiv $FeCl_2$	HCl	0	0

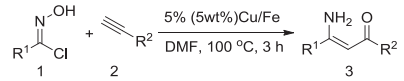
[a] Reaction conditions: 0.25 mmol 3,5-diphenylisoxazole, 0.1 mL DMF, 100 °C.
[b] Conversions were determined by GC–MS.
[c] Reaction with the same Fe content as 5 mol % (5 wt %)Cu/Fe.
[d] Reaction with 1 equiv HCl.
[e] Reaction in DMF bubbled with HCl gas.
[f] Reaction carried out in H_2 atmosphere.

In our model reaction, HCl was formed from hydroximoyl chloride during the formation of nitrile oxide. We supposed that the acid plays crucial role in the ring opening step, therefore we added concentrated HCl aqueous solution to the reaction and the conversion of isoxazole to aminoenone was found to be 30% after 1 h and 65% after 3 h (entry 5). However, we observed earlier that water suppressed the ring opening (Table 2, entry 1). To exclude water from the reaction mixture, we repeated the reaction using HCl gas dissolved in DMF. We observed almost complete reaction after 1 h with copper on iron catalyst (entry 7). Utilization of $FeCl_2$ for the reductive cleavage in DMF(HCl) in the presence and absence of hydrogen gas did not gave the desired aminoenone product. On the basis of these studies we can conclude that the transformation requires the presence of iron metal and HCl.

On the basis of these findings and literature reports, we propose that the first step of the reaction sequence is the copper-catalyzed 1,3-dipolar cycloaddition between the acetylene (**2**) and the in situ generated nitrile oxide.

In the absence of base, the formed HCl byproduct along with the iron promote the reductive ring opening of the isoxazole to the β-aminoenone (**3**) via electron transfer. The aminoenone product then can be transformed into heterocyclic molecules, such as disubstituted pyrazoles (**5**). To demonstrate the applicability of copper on iron under the developed conditions, we synthesized several β-aminoenones from structurally diverse hydroximoyl chlorides and terminal acetylenes (Table 4).

Table 4
Cu/Fe promoted synthesis of aminoenones[a]



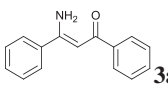
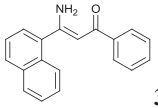
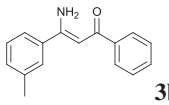
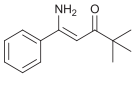
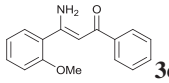
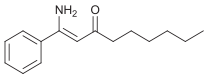
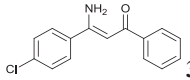
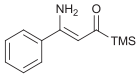
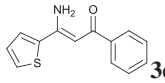
Product	Yield[b] (%)	Product	Yield[b] (%)
 **3a**	71	 **3f**	68

Table 4 (*continued*)

Product	Yield[b] (%)	Product	Yield[b] (%)
 **3b**	50	 **3g**	51
 **3c**	60	 **3h**	44
 **3d**	70	 **3i**	36
 **3e**	57		

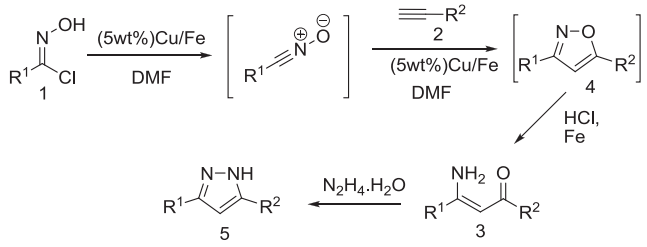
[a] Reaction conditions: 1 mmol hydroximoyl chloride, 1 mmol acetylene, 0.4 mL DMF, 5 mol % (5 wt %)Cu/Fe.
[b] Yields of isolated product after chromatographic purification.

The reaction of phenylacetylene and *N*-hydroxy-benzenecarboximidoyl chloride in DMF at 100 °C gave the appropriate β-aminoenone (**3a**) in 71% yield. Substrates bearing electron donating methyl (**1b**) or methoxy groups (**1c**) on the phenyl ring of hydroximoyl chloride gave the corresponding aminoenones **3b** and **3c** with 50% and 60% yields, respectively. Reaction of chloro-substituted hydroximoyl chloride (**1d**) with phenylacetylene under the optimized reaction conditions afforded the desired product **3d** in 70% yield. Using hydroximoyl chlorides with thiophenyl (**1e**) and naphthyl (**1f**) rings, we obtained the aminoenones (**3e**, **3f**) also with the similar efficiency (57% and 68%). Reactions were also performed with alkyl acetylenes bearing bulky *tert*-butyl and *n*-hexyl groups, and aminoenones **3g** and **3h** were isolated after the ring opening of the alkyl isoxazoles with 51% and 44% yield. The reaction of *N*-hydroxy-benzenecarboximidoyl chloride with trimethylsilylacetylene afforded the TMS substituted aminoenone **3i** in lower yield (36%). Unfortunately, aliphatic hydroximoyl chlorides and internal acetylenes did not provide the desired products under the applied conditions.

While the copper-iron bimetallic system enables the cycloaddition and the subsequent reductive ring opening step under simpler conditions compared to other metal-promoted procedures, some part of the metal additive is sacrificed during the transformation.

We performed the synthesis of **3a** in larger scale, starting from 5 g (32 mmol) of phenylhydroximoyl chloride, and we obtained the product in 62% yield. In this reaction, 2.06 g Cu/Fe was used, while only 602 mg was recovered after the workup. This mass balance is consistent with consumption of some of the iron additive during the reductive N–O bond cleavage.

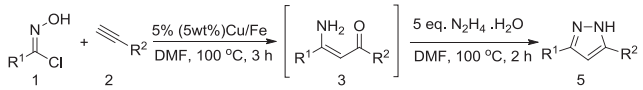
To exploit the reactivity of β-aminoenones, we aimed to prepare nitrogen heterocycles in a one-pot reaction without the isolation of β-aminoenones (Scheme 1). After conducting the previously developed Cu/Fe promoted cycloaddition-reductive ring opening reaction sequence, the addition of hydrazine hydrate to the formed aminoenone should provide 3,5-disubstituted pyrazoles in a one-pot process.

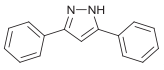
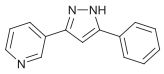
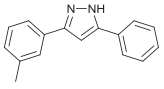
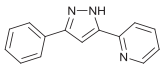
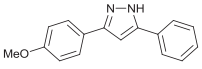
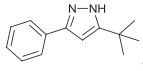
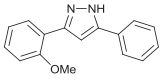
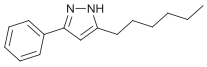
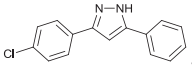
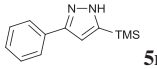
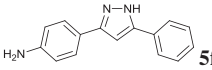
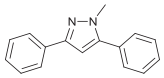
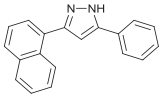
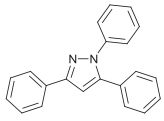
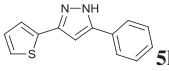


Scheme 1. Proposed reaction steps involving Cu/Fe bimetallic additive.

To demonstrate this transformation, phenylacetylene and *N*-hydroxy-benzenecarboximidoyl chloride were reacted in DMF at 100 °C to provide β-aminoenone (**3a**), then hydrazine hydrate was added into the reaction mixture. To our delight, we observed the formation of the desired 3,5-diphenylpyrazole (**5a**) product in a ring closure step after 2 h reaction time, and the compound was isolated with 70% yield (Table 5). Using this successfully developed reaction sequence, we prepared several 3,5-disubstituted pyrazoles using different hydroximoyl chlorides and acetylenes (Table 5). Methyl-, methoxy, and halogen substituents on the phenyl ring of hydroximoyl chloride did not affect the outcome of the reaction significantly and products (**5b**–**e**) were isolated with 56–74% yield.

Table 5
Sequential one-pot synthesis of pyrazoles[a]



Product	Yield[b] (%)	Product	Yield[b] (%)
 **5a**	70	 **5i**	69
 **5b**	70, 69[c]	 **5j**	46
 **5c**	65	 **5k**	50
 **5d**	74	 **5l**	47
 **5e**	56	 **5m**	44
 **5f**	59[d]	 **5n**	55
 **5g**	58	 **5o**	70
 **5h**	56		

[a] Reaction conditions: 1 mmol hydroximoyl chloride, 1 mmol acetylene, 0.4 mL DMF, 5 mol % (5 wt %) Cu/Fe 100 °C, 3 h, then added 5 mmol hydrazine hydrate, 100 °C, 2 h.
[b] Yields of isolated product after chromatographic purification.
[c] Reaction of *N*-hydroxy-benzenecarboximidoyl chloride and 3-ethynyltoluene.
[d] Reaction of *N*-hydroxy-4-nitrobenzenecarboximidoyl chloride and phenyla cetylene.

3,5-Disubstituted pyrazole **5b** was prepared with the same efficiency either from the reaction of 3-methyl-*N*-hydroxy-benzenecarboximidoyl chloride with phenylacetylene or the reaction of *N*-hydroxy-benzenecarboximidoyl chloride and 3-ethynyltoluene (70% and 69% isolated yield, respectively).

The appropriate pyrazole formation (**5f**) from a nitro-substituted substrate could be also achieved, but reduction of the nitro group to

the amine was observed under the reductive reaction conditions. Naphthyl, thiophenyl, and pyridyl hydroximoyl chlorides all provide the appropriate pyrazoles (**5g**–**i**) with good yields (58%, 56%, 69%, respectively). Beyond phenylacetylene, heteroaromatic, and aliphatic acetylenes as well as trimethylsilylacetylene were also reacted with hydroximoyl chlorides and, followed by the subsequent treatment with hydrazine hydrate, we isolated the appropriate pyrazoles **5j**–**m**. The yields of these products varied in the range of 44–50%. Reactions with methylhydrazine and phenylhydrazine gave 1,2,5-trisubstituted pyrazoles **5n** and **5o** with good yields (55% and 70%).

3. Conclusions

In conclusion, we have developed a simple one-pot procedure for the preparation of β-aminoenones from hydroximoyl chlorides and acetylenes through the reductive ring opening of isoxazole intermediates with the aid of bimetallic copper on iron promoter. The developed procedure employs mild and convenient conditions compared to existing procedures for the preparation of β-aminoenones containing a free NH_2 group. Further treatment of β-aminoenones with hydrazine hydrate gave 3,5-disubstituted pyrazoles in a three step, one-pot sequence.

4. Experimental section

4.1. General

Unless otherwise indicated, all starting materials were obtained from commercial suppliers, and were used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck DC precoated TLC plates with 0.25 mm Kieselgel 60 F_{254}. Visualization was performed with a 254 nm UV lamp. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-250 spectrometer in $CDCl_3$ and DMSO-d_6. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (δ 7.26 for ^1H, δ 77.0 for ^{13}C). Coupling constants (J) are reported in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet). Combination gas chromatography and low resolution mass spectrometry was obtained on an Agilent 6890N Gas Chromatograph (30 m×0.25 mm column with 0.25 μm HP-5MS coating, He carrier gas) and Agilent 5973 Mass Spectrometer (Ion source: EI^+, 70 eV, 230 °C; interface: 300 °C). IR spectra were obtained on a Bruker IFS55 spectrometer on a single-reflection diamond ATR unit. All melting points were measured on Büchi 501 apparatus and are uncorrected. High-resolution mass spectra were acquired on an Agilent 6230 time-of-flight mass spectrometer equipped with a Jet Stream electrospray ion source in positive ion mode. Injections of 0.1–0.3 μl were directed to the mass spectrometer at a flow rate 0.5 ml/min (70% acetonitrile–water mixture, 0.1% formic acid), using an Agilent 1260 Infinity HPLC system. Jet Stream parameters: drying gas (N_2) flow and temperature: 10.0 l/min and 325 °C, respectively; nebulizer gas (N_2) pressure: 10 psi; capillary voltage: 4000 V; sheath gas flow and temperature: 325 °C and 7.5 l/min; TOFMS parameters: fragmentor voltage: 120 V; skimmer potential: 120 V; OCT 1 RF Vpp:750 V. Full-scan mass spectra were acquired over the m/z range 100–2500 at an acquisition rate of 250 ms/spectrum and processed by Agilent MassHunter B.03.01 software. Iron source for Cu/Fe preparation: Sigma–Aldrich Product number: 44,890, Iron puriss ≥99.5% 6–9 μm. DMF Sigma–Aldrich puriss ≥99.5% was used for the reactions.

4.2. Preparation of copper on iron catalyst

A round-bottom flask was charged with iron powder (5.00 g, 89.5 mmol) and H_2O (deoxygenated with argon) (50 mL). The mixture was stirred vigorously with a mechanical stirrer and a solution of $CuSO_4$ (126 mg, 0.79 mmol) in H_2O (50 mL) was added dropwise under argon atmosphere over 1 h, and the stirring was continued for 3 h. The catalyst was separated with a magnet and washed with deoxygenated H_2O (5×20 mL) then acetone (3×20 mL) and dried under reduced pressure.

4.3. General synthesis of aminoenones

A mixture of terminal acetylene (1 mmol, 1 equiv), hydroximoyl chloride (1 mmol, 1 equiv), 5 mol % (5 w/w%) Cu/Fe (64 mg, 0.05 mmol Cu), and DMF (400 μL) were heated for 3 h at 100 °C, then the mixture was diluted with ethyl acetate (5 mL). The catalyst was separated with a magnet and washed with ethyl acetate (4×5 mL) and DCM (2×5 mL). The organic phase was evaporated on Celite and purified by chromatography on silica gel to give the desired product.

4.4. Synthesis of pyrazoles

A mixture of terminal acetylene (1 mmol, 1 equiv), hydroximoyl chloride (1 mmol, 1 equiv), 5 mol % (5 w/w%) Cu/Fe (64 mg, 0.05 mmol Cu), and DMF (400 μL) were heated for 3–4.5 h at 100 °C, then the hydrazine monohydrate was added and the mixture was heated for 2–6 h at 100 °C. After the appropriate time, the reaction mixture was diluted with ethyl acetate (5 mL), the catalyst was separated with a magnet and washed with ethyl acetate (4×5 mL) and DCM (2×5 mL). The organic phase was evaporated on Celite and purified by chromatography on silica gel to give desired pyrazole.

4.5. Synthesis and characterization

4.5.1. 3-Amino-1,3-diphenylprop-2-en-1-one[20] (***3a***). General procedure was followed, yellow oil, 157 mg (0.71 mmol, 71% yield), R_f=0.33 (hexane–ethyl acetate, 4:1), ^1H NMR (250 MHz, $CDCl_3$): δ 10.43 (br s, 1H), 7.97–7.93 (m, 2H), 7.66–7.62 (m, 2H), 7.48–7.43 (m, 6H), 6.15 (s, 1H), 5.53 (br s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 190.1, 162.9, 140.3, 137.6, 131.0, 130.6, 129.0, 128.3, 127.2, 126.3, 91.8, MS (EI, 70 eV): m/z (%): 222 (100, $[M^+]$), 146 (72), 103 (31), 91 (19), 77 (37).

4.5.2. 3-Amino-3-(3-methylphenyl)-1-phenylprop-2-en-1-one (***3b***). General procedure was followed, yellow oil, 119 mg (0.50 mmol, 50% yield), R_f=0.29 (hexane–ethyl acetate, 4:1), ^1H NMR (250 MHz, $CDCl_3$): δ 10.43 (br s, 1H), 7.97–7.94 (m, 2H), 7.48–7.33 (m, 7H), 6.14 (s, 1H), 5.51 (br s, 1H), 2.43 (s, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 190.1, 163.1, 140.4, 138.8, 137.6, 131.4, 130.9, 128.9, 128.2, 127.2, 126.9, 123.4, 91.7, 21.4, MS (EI, 70 eV): m/z (%): 236 (100, $[M^+]$), 160 (77), 117 (55), 91 (20), 77 (69), IR (ATR) 3340, 1519, 1478, 1306, 1230, 747 cm^{-1}, HRMS calcd for $C_{16}H_{16}NO$ $[M+H]^+$ 238.1226 found 238.1230.

4.5.3. 3-Amino-3-(2-methoxylphenyl)-1-phenylprop-2-en-1-one (***3c***). General procedure was followed, yellow solid, 152 mg (0.60 mmol, 60% yield), mp: 92–94 °C, R_f=0.11 (hexane–ethyl acetate, 4:1), ^1H NMR (250 MHz, $CDCl_3$): δ 10.71 (br s, 1H), 7.94–7.91 (m, 2H), 7.57 (dd, 1H, J_1=7.58 Hz, J_2=1.74 Hz), 7.46–7.39 (m, 4H), 7.02 (dd, 2H, J_1=13.90 Hz, J_2=7.58 Hz), 6.25 (br s, 1H), 6.05 (s, 1H), 3.89 (s, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 189.8, 162.0, 156.7, 140.7, 131.5, 130.7, 129.6, 128.1, 127.1, 125.2, 121.1, 111.8, 92.6, 55.8, MS (EI, 70 eV): m/z (%): 252 (7, $[M^+]$), 222 (100), 176 (13), 134 (31), 105 (36), 77 (39), IR (ATR) 1594, 1520, 1241, 1037, 755, 732, 645 cm^{-1}, HRMS calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$ 254.1176 found 254.1183.

4.5.4. 3-Amino-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (***3d***). General procedure was followed, white solid, 181 mg (0.71 mmol, 70% yield), mp: 92–93 °C, R_f=0.32 (hexane–ethyl acetate, 4:1), ^1H NMR (250 MHz, $CDCl_3$): δ 10.37 (br s, 1H), 7.95–7.91 (m, 2H), 7.57 (d, 2H, J=8.5 Hz), 7.48–7.41 (m, 5H), 6.10 (s, 1H), 5.49

(br s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 190.2, 161.5, 140.1, 136.7, 136.0, 131.2, 129.2, 128.3, 127.7, 127.2, 92.0, MS (EI, 70 eV): *m*/*z* (%): 256 (100, [M$^+$]), 180 (44), 137 (23), 117 (22), 89 (14), 77 (32), IR (ATR) 1593, 1527, 1476, 1223, 845, 749, 618 cm^{-1}, HRMS calcd for $C_{15}H_{13}ClNO$ [M+H]$^+$ 258.0680 found 258.0684.

4.5.5. 3-Amino-1-phenyl-3-(thiophen-2-yl)-prop-2-en-1-one (***3e***). General procedure was followed, brown solid, 130 mg (0.57 mmol, 57% yield), mp: 77–79 °C, R_f=0.31 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.96–7.92 (m, 2H), 7.51–7.44 (m, 5H), 7.14–7.11 (m, 1H), 6.27 (s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 190.1, 155.1, 140.1, 139.9, 131.1, 128.3, 128.1, 127.2, 126.5, 91.3, MS (EI, 70 eV): *m*/*z* (%): 228 (100, [M$^+$]), 152 (82), 109 (41), 97 (17), 77 (37), IR (ATR) 3157, 1612, 1592, 1533, 1504, 1223, 716 cm^{-1}, HRMS calcd for $C_{13}H_{11}NNaOS$ [M+Na]$^+$ 252.0454 found 252.0457.

4.5.6. 3-Amino-3-(1-naphthyl)-1-phenylprop-2-en-1-one (***3f***). General procedure was followed, yellow oil, 186 mg (0.68 mmol, 68% yield), R_f=0.33 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.53 (br s, 1H), 8.28–8.24 (m, 1H), 7.94–7.88 (m, 4H), 7.60–7.37 (m, 7H), 6.07 (s, 1H), 5.68 (br s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 190.0, 162.8, 140.0, 135.9, 133.6, 131.1, 130.20, 129.9, 128.4, 128.2, 127.2, 126.9, 126.4, 125.5, 125.15, 125.10, MS (EI, 70 eV): *m*/*z* (%): 272 (21, [M$^+$]), 256 (49), 196 (23), 168 (100), 152 (28), 127 (28), 105 (38), 77 (47), IR (ATR) 3326, 1562, 1519, 1391, 1225, 776, 691 cm^{-1}, HRMS calcd for $C_{19}H_{16}NO$ [M+H]$^+$ 274.1226 found 274.1229.

4.5.7. 1-Amino-4,4-dimethyl-1-phenylpent-1-en-3-one (***3g***).[21] General procedure was followed, off white solid, 103 mg (0.51 mmol, 51% yield), mp: 72–74 °C, lit.: 75 °C, R_f=0.39 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.98 (br s, 1H), 7.57–7.55 (m, 2H), 7.54–7.42 (m, 3H), 5.63 (s, 1H), 5.19 (br s, 1H), 1.21 (s, 9H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 206.5, 161.7, 138.0, 130.3, 128.9, 126.3, 90.7, 42.3, 27.7, MS (EI, 70 eV): *m*/*z* (%): 203 (4, [M$^+$]), 146 (100), 117 (6), 103 (16), 91 (11), 77 (7).

4.5.8. 1-Amino-1-phenylnon-1-en-3-one (***3h***). General procedure was followed, yellow oil, 101 mg (0.44 mmol, 44% yield), R_f=0.39 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.96 (br s, 1H), 7.57–7.54 (m, 2H), 7.46–7.41 (m, 3H), 5.44 (s, 1H), 5.25 (br s, 1H), 2.38 (t, 2H, *J*=7.58 Hz), 1.70–1.58 (m, 2H), 1.30 (s, 6H), 0.88 (t, 3H, *J*=6.48 Hz), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 200.7, 160.8, 137.4, 130.4, 128.9, 126.2, 94.8, 43.0, 31.7, 29.2, 25.9, 22.5, 14.0, MS (EI, 70 eV): *m*/*z* (%): 231 (9, [M$^+$]), 174 (9), 160 (36), 146 (100), 119 (41), 103 (23), 91 (14), IR (ATR) 2925, 1603, 1524, 1484, 150, 694 cm^{-1}, HRMS calcd for $C_{15}H_{21}NNaO$ [M+Na]$^+$ 254.1515 found 254.1521.

4.5.9. 3-Amino-3-phenyl-1-(trimethylsilyl)-prop-2-en-1-one (***3i***). General procedure was followed, yellow solid, 78 mg (0.36 mmol, 36% yield), mp: 93–96 °C, R_f=0.23 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.80 (br s, 1H), 7.38–7.34 (m, 2H), 7.28–7.22 (m, 3H), 5.72 (s, 1H), 5.19 (br s, 1H), 0.00 (s, 9H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 227.7, 158.6, 137.1, 130.7, 129.0, 126.4, 100.9, −2.9, MS (EI, 70 eV): *m*/*z* (%): 218 (20, [M$^+$]), 204 (90), 146 (100), 126 (19), 104 (40), 91 (30), 73 (70), IR (ATR) 1600, 1531, 1480, 1240, 832, 746, 686 cm^{-1}, HRMS calcd for $C_{12}H_{18}NOSi$ [M+H]$^+$ 220.1152 found 220.1156.

4.5.10. 3,5-Diphenyl-1H-pyrazole (***5a***).[22] General procedure was followed (3+2 h), pale yellow solid, 154 mg (0.70 mmol, 70% yield), mp: 196–198 °C, lit.: 200 °C, R_f=0.28 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.73–7.71 (m, 4H), 7.41–7.32 (m, 6H), 6.83 (s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 131.3, 128.8, 128.2, 125.6, 100.1, MS (EI, 70 eV): *m*/*z* (%): 220 (100, [M$^+$]), 191 (23), 104 (11), 77 (14).

4.5.11. 3-m-Tolyl-5-phenyl-1H-pyrazole (***5b***).[23] General procedure was followed (3+2 h), yellow solid, (a) 163 mg (0.70 mmol, 70% yield), (b) 161 mg (0.69 mmol, 69% yield), mp: 127–131 °C, lit.: 145–147 °C, R_f=0.28 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.74–7.70 (m, 2H), 7.50 (d, 2H, *J*=7.74 Hz), 7.37–7.20 (m, 4H), 7.11 (d, 1H, *J*=7.90 Hz), 6.80 (s, 1H), 2.30 (s, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.4, 131.4, 131.0, 128.83, 128.81, 128.7, 128.6, 128.0, 126.3, 125.6, 122.7, 99.9, 21.3, MS (EI, 70 eV): *m*/*z* (%): 234 (100, [M$^+$]), 205 (10), 117 (10), 77 (9).

4.5.12. 3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazole (***5c***).[24] General procedure was followed (3+2 h), pale yellow solid, 163 mg (0.65 mmol, 65% yield), mp: 154–157 °C, lit.: 160 °C, R_f=0.63 (hexane–ethyl acetate, 1:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.70–7.66 (m, 2H), 7.62–7.57 (m, 2H), 7.36–7.26 (m, 3H), 6.86–6.80 (m, 2H), 6.69 (s, 1H), 3.79 (s, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 159.5, 131.5, 128.7, 127.9, 126.9, 125.5, 123.8, 114.1, 99.3, 55.2, MS (EI, 70 eV): *m*/*z* (%): 250 (100, [M$^+$]), 235 (39), 207 (21), 178 (23), 125 (9), 77 (12).

4.5.13. 3-(2-Methoxyphenyl)-5-phenyl-1H-pyrazole (***5d***). General procedure was followed (3+2 h), yellow oil, 186 mg (0.74 mmol, 74% yield), R_f=0.67 (hexane–ethyl acetate, 1:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.95–7.92 (m, 2H), 7.75 (dd, 1H, J_1=7.63 Hz, J_2=1.59 Hz), 7.48–7.42 (m, 2H), 7.38–7.28 (m, 2H), 7.09–7.02 (m, 2H), 6.98 (s, 1H), 3.92 (s, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.8, 151.1, 142.0, 133.3, 129.2, 128.5, 127.8, 127.6, 125.6, 121.3, 117.6, 111.5, 99.9, 55.6, MS (EI, 70 eV): *m*/*z* (%): 250 (100, [M$^+$]), 178 (27), 146 (33), 119 (47), 104 (30), 89 (26), 77 (30), IR (ATR) 1587, 1454, 1244, 1023, 748, 692 cm^{-1}, HRMS calcd for $C_{16}H_{15}N_2O$ [M+H]$^+$ 251.1179 found 251.1186.

4.5.14. 3-(4-Chlorophenyl)-5-phenyl-1H-pyrazole (***5e***).[24] General procedure was followed (3+2 h), white solid, 143 mg (0.56 mmol, 56% yield), mp: 216–217 °C, lit.: 216–218 °C, R_f=0.26 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, DMSO-d_6): δ 13.44 (br s, 1H), 7.84 (s, 4H), 7.48–7.32 (m, 5H), 7.20 (s, 1H), ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 128.7, 126.7, 125.0, 99.8, MS (EI, 70 eV): *m*/*z* (%): 235 (8, [M$^+$]), 254 (100), 225 (13), 189 (15), 94 (17).

4.5.15. 4-(3-Phenyl-1H-pyrazol-5-yl)aniline (***5f***).[25] General procedure was followed (3+4 h), orange solid, 139 mg (0.5 mmol, 59% yield), mp: 162–164 °C, lit.: 163 °C, R_f=0.30 (hexane–ethyl acetate, 1:1), ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.96 (br s, NH), 7.82 (d, *J*=7.27 Hz, 2H), 7.51–7.39 (m, 4H), 7.29 (t, *J*=7.11 Hz, 1H), 6.90 (s, 1H), 6.63 (d, *J*=8.37 Hz, 2H), 5.29 (br s, NH_2), ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 148.6, 128.5, 127.3, 124.9, 113.8, 97.5, MS (EI, 70 eV): *m*/*z* (%): 235 (8, [M$^+$]), 206 (24), 180 (8), 130 (9), 116 (100), 104 (24), 91 (97), 65 (25).

4.5.16. 3-(1-Naphthyl)-5-phenyl-1H-pyrazole (***5g***). General procedure was followed (3+6 h), white solid, 157 mg (0.58 mmol, 58% yield), mp: 134–136 °C, R_f=0.26 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.31–8.27 (m, 1H), 7.91–7.83 (m, 2H), 7.79–7.75 (m, 2H), 7.58–7.31 (m, 7H), 6.87 (s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 149.3, 146.4, 133.8, 131.7, 131.3, 128.97, 128.92, 128.7, 128.3, 128.0, 127.0, 126.6, 126.0, 125.7, 125.4, 125.2, 103.8, MS (EI, 70 eV): *m*/*z* (%): 270 (100, [M$^+$]), 239 (16), 167 (30), 139 (11), 120 (12), 104 (15), IR (ATR) 3218, 1559, 1171, 1073, 963, 758, 685 cm^{-1}, HRMS calcd for $C_{19}H_{15}N_2$ [M+H]$^+$ 271.1230 found 271.1237.

4.5.17. 5-Phenyl-3-(thiophen-2-yl)-1H-pyrazole (***5h***).[22] General procedure was followed (3+2 h), yellow solid, 127 mg (0.56 mmol, 56% yield), mp: 172 °C, R_f=0.26 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.65–7.62 (m, 2H), 7.31–7.19 (m, 5H), 7.00–6.96 (m, 1H), 6.66 (s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 135.0, 130.8, 128.8, 128.3, 127.5, 125.5, 124.7, 124.1, 99.9, MS (EI, 70 eV): *m*/*z* (%): 226 (100, [M$^+$]), 197 (31), 165 (10), 152 (10), 77 (10).

4.5.18. 5-Phenyl-3-(3-pyridyl)-1H-pyrazole (***5i***).[26] General procedure was followed (3+2 h), off white solid, 104 mg (0.47 mmol,

47% yield), mp: 186–188 °C, lit.: 187–188 °C, R_f=0.16 (hexane–ethyl acetate, 1:1), ^{1}H NMR (250 MHz, DMSO-d_6): δ 9.08 (s, 1H), 8.53 (s, 1H), 8.20 (d, 1H, J=8.06 Hz), 7.84 (d, 2H, J=7.42 Hz), 7.50–7.31 (m, 5H), ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 146.3, 132.1, 128.8, 125.0, 123.7, 100.0, MS (EI, 70 eV): m/z (%): 221 (100, [M$^+$]), 192 (14), 77 (14), 51 (13).

*4.5.19. 3-(Phenyl)-5-(2-pyridyl)-1H-pyrazole (**5j**).*[27] General procedure was followed (3+2 h), pale yellow solid, 101 mg (0.46 mmol, 46% yield), mp: 143–144 °C, lit.: 159 °C, R_f=0.19 (hexane–ethyl acetate, 1:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.70 (d, 1H, J=4.90 Hz), 7.90–7.75 (m, 4H), 7.47–7.24 (m, 4H), 7.08 (s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 149.4, 148.7, 137.0, 132.5, 128.7, 128.0, 125.7, 122.9, 120.1, 100.4, MS (EI, 70 eV): m/z (%): 221 (100, [M$^+$]), 192 (67), 165 (15), 115 (16).

*4.5.20. 5-Phenyl-3-tert-butyl-1H-pyrazole (**5k**).*[24] General procedure was followed (3+2 h), white solid, 100 mg (0.50 mmol, 50% yield), mp: 104–106 °C, R_f=0.26 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.80–7.76 (m, 2H), 7.44–7.32 (m, 3H), 6.42 (s, 1H), 1.40 (s, 9H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 132.7, 128.8, 128.6, 128.3, 127.7, 125.5, 98.8, 31.3, 30.3, MS (EI, 70 eV): m/z (%): 200 (33, [M$^+$]), 185 (100), 158 (13), 145 (11), 77 (10).

*4.5.21. 5-Hexyl-3-phenyl-1H-pyrazole (**5l**).*[22] General procedure was followed (3+2 h), yellow solid, 107 mg (0.47 mmol, 47% yield), mp: 69–70 °C, R_f=0.26 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.0 (br s, 1H), 7.76–7.73 (m, 2H), 7.39–7.29 (m, 3H), 6.35 (s, 1H), 2.59 (t, 2H, J=8.10 Hz), 1.62–1.59 (m, 2H), 1.26 (m, 6H), 0.89 (s, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 132.8, 128.6, 127.7, 125.7, 100.9, 31.5, 29.2, 28.9, 26.3, 22.5, 14.0, MS (EI, 70 eV): m/z (%): 228 (18, [M$^+$]), 171 (42), 158 (100), 128 (17).

*4.5.22. 3-Phenyl-5-trimethylsilyl-1H-pyrazole (**5m**).*[28] General procedure was followed (8 h), white solid, 95 mg (0.44 mmol, 44% yield), mp: 123 °C, R_f=0.35 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.78–7.74 (m, 2H), 7.35–7.28 (m, 2H), 7.25–7.18 (m, 1H), 6.65 (s, 1H), 0.24 (s, 9H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 151.9, 144.3, 133.3, 128.6, 127.6, 125.9, 109.8, −1.24, MS (EI, 70 eV): m/z (%): 216 (69, [M$^+$]), 201 (100), 185 (14), 100 (16).

*4.5.23. 1-Methyl-3,5-diphenyl-1H-pyrazole (**5n**).*[29] General procedure was followed (8 h), white solid, 115 mg (0.55 mmol, 55% yield), mp: 58–59 °C, lit.: 54–57 °C, R_f=0.53 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.87–7.84 (m, 2H), 7.48–7.32 (m, 8H), 6.63 (s, 1H), 3.94 (s, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 150.5, 145.0, 133.4, 130.6, 128.7, 128.67, 128.6, 128.5, 127.6, 125.5, 103.2, 37.7, MS (EI, 70 eV): m/z (%): 234 (100, [M$^+$]), 189 (8), 130 (10), 118 (10), 103 (11), 77 (18).

*4.5.24. 1,3,5-Triphenyl-1H-pyrazole (**5o**).*[22] General procedure was followed (8 h), white solid, 115 mg (0.70 mmol, 70% yield), mp: 136–137 °C, lit.: 140–142 °C, R_f=0.75 (hexane–ethyl acetate, 4:1), ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.02 (d, 2H, J=7.4 Hz), 7.48–7.42 (m, 5H), 7.37–7.31 (m, 8H), 6.87 (s, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 151.9, 144.4, 140.1, 133.0, 130.6, 128.9, 128.7, 128.6, 128.4, 128.3, 128.0, 127.4, 125.8, 125.3, 105.2, MS (EI, 70 eV): m/z (%): 296 (100, [M$^+$]), 192 (11), 165 (17), 77 (36).

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Supplementary data

Experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra for the products are available. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.08.047.

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