Synthesis of pyrazolines by a site isolated resin-bound reagents methodology†

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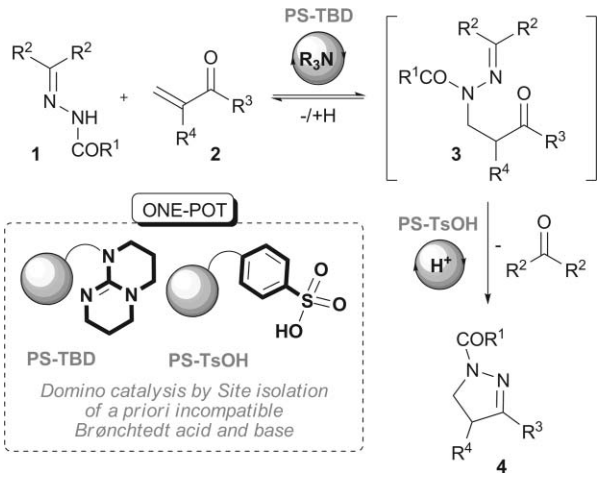
The elaboration of biologically important 3,4-substituted pyrazolines was achieved by an organocatalysed aza-Michael/transimination domino sequence between hydrazones and enones making use of a mixture of heterogeneous resin-bound acid/base reagents. This methodology nicely illustrates the site isolation concept of supported reagents allowing the simultaneous use of otherwise destructive reactive functionalities.

Introduction

Supported heterogeneous reagents have been emerging as useful tools in parallel solution-phase synthesis of chemical libraries in medicinal chemistry, facilitating work-up and scavenging of side-products by simple filtration, and, last but not least, allowing continuous flow synthetic transformations.[1]

At the beginning of the seventies, another unique capability of resin-bound reagents was pioneered by Cohen, Kraus and Patchornik.[2] They carried out multistep reactions by means of two supported reagents in the same pot having incompatible functional groups *e.g.* an acid and a base being, however, isolated to each other by their surrounding polymeric matrix.[3] Thereby, the different reactants diffuse from one resin to the other to undergo successive chemical transformations. At the same period of time, the potential of the so-called "site isolation concept" was also highlighted for anchoring two metal catalysts by Pittman or for the detection of reactive intermediates by Rebek and co-workers.[4] Stowell and Hauck made use of mixed ion-exchange resins allowing concurrent acid/base catalysis in the same flask affording an improved synthesis of cyclopentenones by driving an otherwise unfavorable equilibrium.[5] Subsequently, many research groups focused on the ingenious construction of multifunctional polymeric architectures and they exemplified their use on simple model domino reactions as proof-of-principal.[6] Interestingly, Kudo and co-workers reported an asymmetric sequential acid/base promoted aldolisation by means of a chiral supported peptide.[7] Recently, Dixon and co-workers elevated this strategy to construct rather advanced aza-heterocyclic frameworks by elegant one-pot acid–base catalysed cyclization cascades promoted by a mixture of isolated reagents on polystyrene (PS) beads.[8] In the line of these elegant precedents, the prospects for the development of domino transformations by means of simultaneous use of antagonist resin-bound reagents afford unprecedented opportunities in organic synthetic chemistry.

In this paper, we are delighted to report on an acid–base site isolation strategy providing an innovative and practical means to rapidly construct 3,4-substituted pyrazoline derivatives **4** (Scheme 1). This heterocyclic platform,[9] having a polar functional group on nitrogen such as acyl COR^1,[10] has shown promises in current drug development with insecticidal properties,[11a] as an inhibitor of parasitic trypanosomal infections,[11b] as progesterone receptor ligands,[11c] and finally as cannabinoid CB1 receptor antagonists.[11d–e] We envisaged a base-catalysed aza-Michael addition of hydrazones **1** to terminal enones **2**, followed by an acid-catalysed transimination reaction (**3** to **4**).[12] The use of readily available hydrazones to eventually deliver monosubstituted hydrazines within the pyrazoline framework offers several advantages: (1) protection of the hydrazine primary amine to achieve a selective alkylation on NH^1; (2) modulation of the nucleophilic character of the amide moiety with respect to R^2; (3) masking the hydrazine as a less basic hydrazone preventing the immobilisation of the nucleophile **1** or product **3** onto the acidic polymer and allowing the diffusion of compounds between the two resins to perform the multistep acid/base catalysis. Thereby, a straightforward organocatalytic[13] domino methodology was conveniently carried out in a one-pot fashion by means of a mixture of commercially available supported heterogeneous tosic acid (PS-TsOH, Amberlyst® A15) and PS-TBD



Scheme 1 Working strategy for domino synthesis of pyrazolines.

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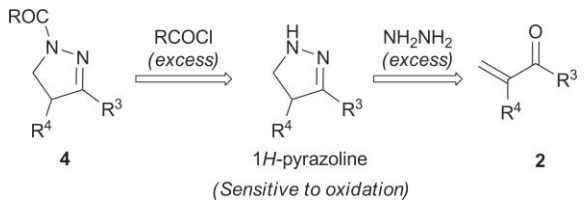
(1,5,7-triazabicyclo[4.4.0]dec-5-ene) providing the isolated product by simple filtration, thus facilitating the construction of chemical libraries.[8,14]

Results and discussion

Context and preliminary results in homogeneous phase

The preparation of 3,4-substituted pyrazolines **4** (Scheme 2) is usually carried out in two steps *via* the condensation of hydrazine onto terminal enones **2** to form intermediate 1*H*-pyrazolines followed by the addition of acyl chlorides, isocyanates, *etc.*[11] First of all, the low stability of enone precursors **2** and the sensitivity of the 1*H*-pyrazoline intermediates toward oxidative events requires the rapid execution of these steps, together with the use of an excess of chemicals.



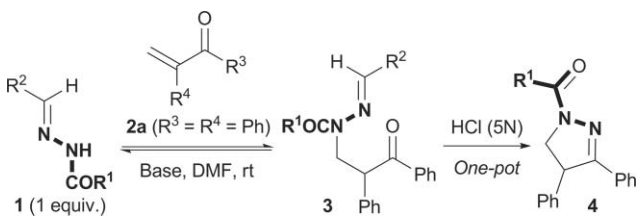
Scheme 2 Regular strategy.

Alternatively (Table 1), Shi and co-workers disclosed a sequential one-pot formation of *N*-benzoyl-4,5-dihydropyrazoles **4** from readily available hydrazones **1** and a limited array of unsubstituted simple enones **2** (R^4 = H, R^3 = Me, Ph).[12] This elegant organocatalytic sequence proceeded under the influence of a catalytic amount of DABCO (**2** to **3**) followed by an acidic work-up (**3** to **4**) but required several days for completion.[15] Seeking an expeditious strategy for the elaboration of bioactive 3,4-substituted pyrazolines (Table 1), we evaluated this methodology on the more substituted enone **2a** (R^4 = Ph, R^3 = Ph). In our hands, DABCO performed poorly (entry 1) and stronger bases such as DBU (entry 4 *vs.* entries 1–3) or TBD guanidine (entry 5) were required to achieve the conjugated addition reaction of *N*-benzoyl hydrazone **1a** to compounds **3a**. A maximum of 64% conversion into the aza-Michael product **3a** was obtained (entry 5) irrespective to the reaction time (entry 6) or excesses of hydrazone **1a** (entry 7). Making use of the more nucleophilic or less acidic *N*-acetyl hydrazone **1b** (entry 8) or **1c** (entry 9) an almost complete transformation into adduct **3b** was achieved. As a matter of fact, the equilibrium between enone **2a** and aza-Michael products **3** is finely balanced with respect to the hydrazone structure (COR^1 = COMe **1a** *vs.* COPh **1b**), likely related to the thermodynamic stability of the corresponding anions. This phenomenon engenders the decomposition of the aza-Michael products **3** over time limiting the scope of the reaction. Moreover, the overall yields of pyrazolines **4** (entries 7–9), obtained by cyclization of the precursor **3** under acidic conditions, are limited to the conversion of enone **1** during the equilibrated aza-Michael process. Accordingly, we anticipated that the use of a mixture of polymer supported reagents isolating antagonist acid and base functional groups would afford a unique opportunity to drive the reactions to completion by achieving both the aza-Michael and the cyclization steps in the same pot.[16]

Use of supported reagents

In order to probe the requirement of a hydrazone in this strategy (Table 2), we performed test reactions with acetylhydrazine (entries 1 and 2) and enone **2a**. No significant formation of pyrazoline **4b** took place in the presence of a base or an acid although the enone **2a** was completely consumed.[17] Next, it was shown that neither the polystyrene supported base (PS-TBD) in the presence of TsOH (entry 3), nor the mixture of PS-TsOH and TBD base (entry 4) effected the domino transformations into pyrazoline **4b**. In both cases, the acid and base cancelled out each other thus hampering any acido-basic catalysis to occur. On the contrary, the mixture of supported reagents (entry 5), smoothly furnished the corresponding *N*-acetylpyrazoline in 55% yield demonstrating

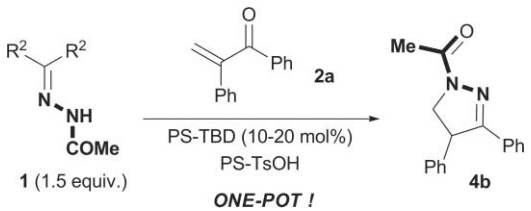
Table 1 Initial attempts in homogeneous conditions



Entry	**1** R^1, R^2	Base (20 mol%)	Time/h	Conversion to **3** [a](NMR Yield, %)[b]	**4** [c](%)
1	Ph, Ph (**1a**)	DABCO	48	1 (**3a**)	—
2	Ph, Ph (**1a**)	Quinuclidine	48	10 (**3a**)	—
3	Ph, Ph (**1a**)	DMAP	48	4 (**3a**)	—
4	Ph, Ph (**1a**)	DBU	48	60 (**3a**)	—
5	Ph, Ph (**1a**)	TBD[d]	48	64 (**3a**)	—
6	Ph, Ph (**1a**)	TBD[d]	3	62 (**3a**)	—
7	Ph, Ph (**1a**)[e]	TBD[d]	3	58 (43, **3a**)	42 (**4a**)
8	Me, Ph (**1b**)[e]	TBD[d]	3	95% (83, **3b**)[f]	67 (**4b**)
9	Me, Me (**1c**)[e]	TBD[d]	3	95% (61, **3b**)	55 (**4b**)

[a] Determined by NMR. [b] NMR yield with an internal standard. [c] Isolated yield by column chromatography from **1**. [d] 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [e] 1.5 equiv. [f] 81% of isolated yield by column chromatography from 0.5 mmol of enone **2a**.

Table 2 Optimisation of the addition reaction of acetylhydrazone **1** to enone **2a**[a]



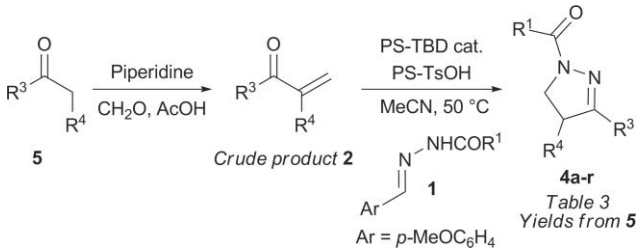
Entry	Hydrazone **1** (R^2,R^2)	Base (20 mol%)	Acid (1 equiv.)	Pyrazoline **4b** (%)[b]
1	($AcNHNH_2$)[c]	PS-TBD	—	<10
2	($AcNHNH_2$)[c]	—	PS-TsOH	0
3	Me,H (**1c**)	PS-TBD	$TsOH,H_2O$	0
4	Me,H (**1c**)	TBD	PS-TsOH	0
5	Me,H (**1c**)	PS-TBD	PS-TsOH	55
6	Me,H (**1c**)	PS-TBD	PS-TsOH[d]	33
7	Me,H (**1c**)	PS-TBD	PS-TsOH[e]	25
8	Et,H (**1d**)	PS-TBD	PS-TsOH	62
9	Me,Me (**1e**)	PS-TBD	PS-TsOH	52
10	Ph,H (**1f**)	PS-TBD	PS-TsOH	73
11	4-$MeOC_6H_4$,H (**1g**)	PS-TBD	PS-TsOH	78
12	4-$MeOC_6H_4$,H (**1g**)	PS-TBD[f]	PS-TsOH	51
13	4-$MeOC_6H_4$,H (**1g**)	PS-TBD[g]	PS-TsOH	77

[a] All reactions were performed with 0.5 mmol of freshly prepared enone **2a** (1 M), acetylhydrazone (1.5 equiv.) and a mixture of polystyrene resin reagents in anhydrous acetonitrile at 50 °C for 24 h. [b] NMR yield with an internal standard. [c] $AcNHNH_2$ (1.5 equiv.) [d] 0.4 equiv. of PS-TsOH, 27% of aza-Michael product **3a** is obtained. [e] 25 °C. [f] 1 equiv. H_2O, 26% of enone not transformed. [g] 10 mol% of PS-TBD.

an acid–base site isolation catalysis in action while allowing a convenient work-up by filtration. The overall process was retarded by decreasing the amount of acid to 0.4 equivalents (entry 6) or by working at room temperature (entry 7). The use of hydrazones diversely substituted at the imine moiety affords opportunities to tune the nucleophilic character of these acylhydrazine analogues which are eventually delivered to enones. Hydrazones derived from an aliphatic aldehyde (entry 8) or ketone (entry 9) were evaluated but only in the former case the yield of **4b** was slightly improved. Eventually, the best results were obtained by means of more robust hydrazones **1f** formed with aromatic aldehydes (entry 10), and electron-rich *para*-anisaldehyde derived hydrazones **1g** affording up to 78% yield (entry 11). The catalytic amount of PS-TBD could be reduced to 0.1 equivalents without affecting the outcome of the reaction over 24 h (entry 13). However, the addition of one equivalent of water, with the hope to accelerate the hydrolysis of the hydrazone moiety after the aza-Michael addition, slowed down the transformation into pyrazoline (entry 12). At this stage, the exact mechanism of the cyclization events, *i.e.* either a hydrolysis of the hydrazone **3** moiety into hydrazine followed by a cyclocondensation step or the direct cyclization of the hydrazone to the ketone function, is not clear.

Subsequently, we evaluated the scope of this straightforward one-pot pyrazoline synthesis with hydrazones **1** derived from *para*-anisaldehyde and commercially available hydrazines (Table 3). The rather unstable enones **2** were freshly prepared in quantitative crude yield by a standard Mannich type methylenation/elimination sequence of the corresponding ketones **5**.[18] Being used subsequently without further purification, the reported yields correspond therefore to a three steps process from ketone **5**. First of all, it was demonstrated that the domino reaction performed well with various *N*-acyl (entries 1–3), carbamate (entry 4) and semicarbazide (entry 5) type hydrazones affording the corresponding pyrazolines **4** in 74 to 82% yields. Importantly, the reaction furnishing the pyrazoline flanked by a Cbz group (entry 4) could be performed on 4 mmol scale without affecting the yield. The *N*-tosylhydrazone **1j** furnished the corresponding pyrazoline (entry 6) along with an inseparable aza-Michael product arising from the conjugated addition of the $TsNHNH_2$. One can suppose that the cyclization step into pyrazoline is hampered by the strong electron-withdrawing character of the tosyl group, releasing meanwhile the tosylhydrazine through hydrolysis of the corresponding hydrazone. A limitation of this process was shown with 4-acylpyridinehydrazones **1k**. This failure might be due to the protonation/immobilization of **1k** by the acidic PS-TsOH resin which led to a complete decomposition of substrates (entry 7). The different *N*-substituted hydrazones were successfully added to enones bearing various substituted electron-poor or electron-rich aromatic phenyl or heterocyclic rings to afford the corresponding 3,4-diarylpyrazolines in more than 71% yield (entries 8–15). The aza-Michael/transimination sequence performed well with α-alkyl substituted enones extending the scope of this methodology (entries 16). Furthermore, enones whose carbonyl moiety is flanked by a pendant alkyl group underwent a smooth transformation into *N*-Bz pyrazoline **4q** (entry 17) and *N*-CONHPh pyrazoline **4r** (entry 18) with 75% and 80% yields respectively. Taken all together, this methodology provide an easy access to 3,4-substituted-Δ^2-pyrazoline derivatives having one or two aromatic groups and various polar functional groups on nitrogen. Thanks to the site isolation concept allowing the presence of both basic and acidic functionality in the same pot driving the equilibrated aza-Michael reaction towards the subsequent pyrazolines formation regardless to the nature of hydrazones or enones. Consequently, this domino process avoids tedious and time-consuming optimization for each substrate.

Table 3 Addition of various hydrazones **1** to enone **2**[a]

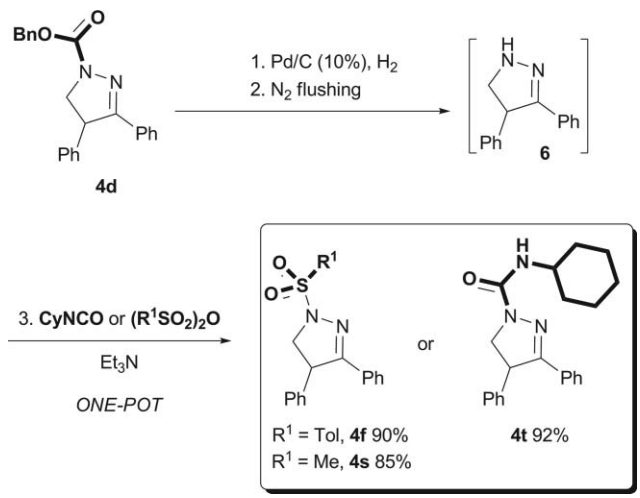


Entry	Hydrazone (COR^1)	Enone **2** (R^3)	Enone **2** (R^4)	Pyrazoline **4** (%)[b]
1	COPh (**1f**)	Ph	Ph	74 (**4a**)
2	COMe (**1e**)	Ph	Ph	77 (**4b**)
3	CO-2-furanyl (**1g**)	Ph	Ph	73 (**4c**)
4	COOBn (**1h**)	Ph	Ph	82 (**4d**)[c]
5	CONHPh (**1i**)	Ph	Ph	82 (**4e**)
6	(Ts) (**1j**)	Ph	Ph	56 (**4f**)[d]
7	CO-4-Pyr (**1k**)	Ph	Ph	0 (**4g**)
8	COMe (**1e**)	4-ClC_6H_4	Ph	72 (**4h**)
9	CONHPh (**1i**)	4-ClC_6H_4	Ph	75 (**4i**)
10	COOBn (**1h**)	4-ClC_6H_4	Ph	77 (**4j**)
11	COMe (**1e**)	4-FC_6H_4	Ph	74 (**4k**)
12	COOBn (**1h**)	4-FC_6H_4	Ph	78 (**4l**)
13	COMe (**1e**)	4-$MeOC_6H_4$	4-$MeOC_6H_4$	70 (**4m**)
14	COMe (**1e**)	2-thienyl	Ph	71 (**4n**)
15	CONHPh (**1i**)	2-thienyl	Ph	75 (**4o**)
16	COMe (**1e**)	Ph	Me	65 (**4p**)
17	COPh (**1f**)	*i*-Pr	Ph	75 (**4q**)
18	CONHPh (**1i**)	*i*-Pr	Ph	80 (**4r**)

[a] All reactions were performed with 0.5 mmol of freshly prepared enones **2** (1 M), *para*-anisaldehyde derived hydrazone **1** (1.5 equiv.) and a mixture of polystyrene resin PS-TBD (20 mol%) and PS-TsOH (1 equiv.) in anhydrous acetonitrile at 50 °C for 16–22 h. [b] Isolated yield after column chromatography. [c] Performed on 4 mmol scale. [d] NMR yield with an internal standard.

One-pot transprotection

As demonstrated in the previous scope and limitation study, the addition/cyclization reaction sequence of *N*-tosylhydrazone **1j** did not perform well. Nevertheless, we developed a straightforward one-pot transprotection protocol (Scheme 3) from readily available and stable *N*-benzyloxycarbonyl pyrazoline **4d** (Table 3, entry 4). The introduction of various tosyl or mesyl pendants was achieved after palladium catalysed hydrogenolysis of the Cbz protective group preventing, thereby, the isolation of the unstable 1*H*-pyrazoline **6**. In the same manner, the addition reaction of an isocyanate proceeded smoothly to afford the corresponding amide **4t**. Therefore, more elaborate functionality could be introduced lately on nitrogen N^1 to elaborate more complex pyrazolines.



Scheme 3 One-pot transprotection.

Conclusions

In summary, we achieved a straightforward site isolated base (0.2 equiv. PS-TBD) and acid (1 equiv. PS-TsOH) protocol yielding a wide variety of 3,4-substituted pyrazolines making use of the modified Shi's masked hydrazine methodology.[12] This metal free domino process promoted by commercially available supported reagents not only facilitates the work-up by means of a simple filtration protocol but allows the facile formation of chemical libraries of these biologically relevant nitrogen-containing heterocycles.

Experimental

General

Chromatographic purification of compounds was achieved with 60 silica gel (40–63 μm).‡ Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or phosphomolybdic acid or $KMnO_4$ oxidation. ^1H NMR

‡ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

spectra were recorded at 300 MHz on a Bruker AVANCE 300. Data appear in the following order: chemical shifts in ppm, number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant *J* in Hz. ^{13}C NMR spectra were acquired at 75.4 MHz operating with broad band ^{1}H decoupling. The hydrogen multiplicity was obtained by DEPT135 or Attached Proton Test (APT) using JMOD pulse program. IR spectra were recorded on a Perkin Elmer IRTF 1650 spectrometer with solid dispersed on KBr pastille. Mps stand uncorrected. The hydrazones were synthesized with respect to known procedures and used without further purification.[19] TBD bound to polystyrene crosslinked with 2% DVB (2.5 mmol g^{-1}) provided by Fluka and Amberlyst ® 15 (dry, ≥ 4.7 eq/kg) were used as received.

Representative procedure for the synthesis of (3,4-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone 4a. To a stirred solution of freshly prepared 1,2-diphenylprop-2-en-1-one **2a** (104.1 mg, 0.50 mmol) and hydrazone **1f** (0.75 mmol) in anhydrous acetonitrile (0.5 mL) was added PS-TBD (40.0 mg, 0.10 mmol), and Amberlyst® A-15 (106.0 mg, 0.50 mmol). The resulting mixture was smoothly magnetically stirred and heated at 50 °C until the disappearance of starting material on TLC. After cooling, the polymers were removed by filtration and the resin was washed with dichloromethane. The filtrate was concentrated *in vacuo* and purified by flash column chromatography to furnish pyrazoline **4a** as described in the following characterizations. *Remark*: the obtained solids tend to retain solvents such as AcOEt or CH_2Cl_2, so they have to be dried for a long period of time under vacuum.

(3,4-Diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (4a). Reaction time: 18 h; white solid (120.6 mg, 74%); R_f 0.61 (Petroleum ether/EtOAc: 1/1); mp 50–52 °C; IR (KBr) ν_{max}/cm^{-1} 1636, 1575, 1492, 1450, 1420, 1317, 1144, 825, 758, 690; δ_H(300 MHz; $CDCl_3$) 8.07–8.05 (2 H, m), 7.63–7.22 (13 H, m), 4.74 (1 H, dd, *J* 11.5 and *J* 4.9), 4.60 (1 H, dd, *J* 12.0 and *J* 11.6), 4.24 (1 H, dd, *J* 12.0 and *J* 4.9); δ_C(75.4 MHz; $CDCl_3$) 167.0 (C), 157.8 (C), 140.4 (C), 134.2 (C), 131.1 (CH), 130.7 (C), 130.2 (CH), 130.1 (CH), 129.4 (CH), 128.6 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 55.7 (CH_2), 50.0 (CH); HRMS (EI+) calcd for $C_{22}H_{18}N_2O$: 326.1419; Found: 326.1417.

1-(3,4-Diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (4b). Reaction time: 18 h; white solid (101.6 mg, 77%); R_f 0.23 (Petroleum ether/EtOAc: 2/1); mp 106–107 °C; IR (KBr) ν_{max}/cm^{-1} 1659, 1586, 1557, 1458, 1444, 1419, 1362, 1228, 1154, 1044, 952, 848, 762, 701, 691; δ_H(300 MHz; $CDCl_3$) 7.66–7.63 (2 H, m), 7.31–7.15 (8 H, m), 4.70 (1 H, dd, *J* 11.5 and *J* 5.0), 4.37 (1 H, dd, *J* 12.0 and *J* 11.6), 4.02 (1 H, dd, *J* 12.0 and *J* 5.0), 2.47 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 169.6 (C), 156.9 (C), 140.4 (C), 130.8 (C), 130.0 (CH), 129.4 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 126.0 (CH), 54.3 (CH_2), 50.8 (CH), 21.7 (CH_3); HRMS (EI+) calcd for $C_{17}H_{16}N_2O$: 264.1262; Found: 264.1249.

(3,4-Diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(furan-2-yl)methanone (4c). Reaction time: 22 h; white solid (115.7 mg, 73%); R_f 0.25 (Petroleum ether/EtOAc: 2/1); mp 134–136 °C; IR (KBr) ν_{max}/cm^{-1} 1635, 1557, 1473, 1436, 1318, 1226, 1155, 1082, 1017, 808, 757, 699; δ_H(300 MHz; $CDCl_3$) 7.73–7.67 (4 H, m), 7.34–7.19 (8 H, m), 6.61 (1 H, dd, *J* 3.5 and *J* 1.7), 4.73 (1 H, dd, *J* 11.5 and *J* 4.9), 4.57 (1 H, dd, *J* 12.2 and *J* 11.5), 4.23 (1 H, dd, *J* 12.2 and *J* 4.9); δ_C(75.4 MHz; $CDCl_3$) 158.4 (C), 156.4 (C), 146.3 (C), 145.6 (CH), 140.2 (C), 130.7 (C), 130.3 (CH), 129.5 (CH), 128.7 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 119.1 (CH), 111.7 (CH), 55.3 (CH_2), 49.8 (CH); HRMS (ESI+): Calcd for $C_{20}H_{17}N_2O_2$ [M+H]+: 317.1290; Found: 317.1300.

Benzyl 3,4-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (4d). Reaction time: 16 h; white solid (146.4 mg, 82%); R_f 0.24 (Petroleum ether/EtOAc: 3/1); mp 132–133 °C; IR (KBr) ν_{max}/cm^{-1} 1714, 1446, 1408, 1373, 1299, 1164, 1127, 980, 844, 754, 686; δ_H(300 MHz; $CDCl_3$) 7.61–7.58 (2 H, m), 7.36–7.09 (13 H, m), 5.23 (2 H, br s), 4.61 (1 H, dd, *J* 11.5 and *J* 5.2), 4.29 (1 H, dd, *J* 11.3 and *J* 11.2), 3.88 (1 H, dd, *J* 11.2 and *J* 5.1); δ_C(75.4 MHz; $CDCl_3$) 156.7 (C), 152.0 (C), 140.1 (C), 136.1 (C), 130.5 (C), 129.8 (CH), 129.2 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 67.7 (CH_2), 55.6 (CH_2), 51.0 (CH); HRMS (ESI+): Calcd for $C_{23}H_{21}N_2O_2$ [M+H]+: 357.1603; Found: 357.1613.

***N*,3,4-Triphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (4e).** Reaction time: 16 h; white solid (140.3 mg, 82%); R_f 0.48 (Petroleum ether/EtOAc: 2/1); mp 185–187 °C; (lit.,[18a] 185 °C); IR (KBr) ν_{max}/cm^{-1} 3283, 1636, 1591, 1560, 1515, 1471, 1444, 1386, 1323, 1296, 1228, 1159, 1109, 741, 693; δ_H(300 MHz; $CDCl_3$) 8.18 (1 H, s), 7.65–7.56 (4 H, m), 7.37–7.04 (11 H, m), 4.76 (1 H, dd, *J* 11.7 and *J* 5.2), 4.43 (1 H, dd, *J* 11.6 and *J* 11.3), 4.09 (1 H, dd, *J* 11.3 and *J* 5.1); δ_C(75.4 MHz; $CDCl_3$) 155.0 (C), 152.1 (C), 140.3 (C), 138.6 (C), 130.7 (C), 129.9 (CH), 129.4 (CH), 129.1 (CH), 128.7 (CH), 127.8 (CH), 127.4 (CH), 127.1 (CH), 123.1 (CH), 119.1 (CH), 54.6 (CH_2), 51.4 (CH); HRMS (ESI+): Calcd for $C_{22}H_{20}N_3O$ [M+H]+: 342.1606; Found: 342.1604.

1-(3-(4-Chlorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-ethanone (4h). Reaction time: 21 h; white solid (107.7 mg, 72%); R_f 0.14 (Petroleum ether/EtOAc: 3/1); mp < 50 °C; IR (KBr) ν_{max}/cm^{-1} 1667, 1585, 1557, 1495, 1444, 1400, 1359, 1309, 1227, 1170, 1091, 1011, 953, 834, 761, 710; δ_H(300 MHz; $CDCl_3$) 7.51–7.47 (2 H, m), 7.26–7.14 (5 H, m), 7.08–7.05 (2 H, m); 4.59 (1 H, dd, *J* 11.9 and *J* 5.4), 4.31 (1 H, dd, *J* 11.9 and *J* 12.1), 3.94 (1 H, dd, *J* 12.2 and *J* 5.4), 2.39 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 169.5 (C), 155.7 (C), 140.1 (C), 135.9 (C), 129.5 (CH), 129.3 (C), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.3 (CH), 54.4 (CH_2), 50.8 (CH), 21.7 (CH_3); HRMS (ESI+): Calcd for $C_{17}H_{16}N_2OCl$ [M+H]+: 299.0951; Found: 299.0948.

3-(4-Chlorophenyl)-*N*,4-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (4i). Reaction time: 17 h; white solid (141.1 mg, 75%); R_f 0.28 (Petroleum ether/EtOAc: 3/1); mp 164–166 °C; (lit.,[18a] 157 °C); IR (KBr) ν_{max}/cm^{-1} 3387, 1686, 1593, 1526, 1445, 1381, 1309, 1225, 1149, 1091, 829, 790, 742, 695; δ_H(300 MHz; $CDCl_3$) 8.12 (1 H, s), 7.60–7.57 (4 H, m), 7.37–7.06 (10 H, m), 4.72 (1 H, dd, *J* 11.7 and *J* 5.4), 4.40 (1 H, t, *J* 11.5), 4.09 (1 H, dd, *J* 11.3 and *J* 5.4); δ_C(75.4 MHz; $CDCl_3$) 153.9 (C), 152.0 (C), 140.0 (C), 138.5 (C), 135.9 (C), 129.5 (CH), 129.2 (C), 129.1 (CH), 129.0 (CH), 128.4 (CH), 128.0 (CH), 127.4 (CH), 123.3 (CH), 119.2 (CH), 54.7 (CH_2), 51.3 (CH); HRMS (ESI+): Calcd for $C_{22}H_{19}N_3OCl$ [M+H]+: 376.1217; Found: 376.1216.

Benzyl 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (4j). Reaction time: 21 h; white solid (150.7 mg, 77%); R_f 0.37 (Petroleum ether/EtOAc: 3/1); mp <50 °C; IR (KBr) ν_{max}/cm^{-1} 1724, 1593, 1417, 1291, 1164, 1123, 1087, 967,

826, 758, 698; δ_H(300 MHz; $CDCl_3$) 7.53–7.50 (2 H, m), 7.35–7.07 (12 H, m), 5.23 (2 H, s), 4.58 (1 H, dd, *J* 11.6 and *J* 5.4), 4.31 (1 H, t, *J* 11.5), 3.89 (1 H, dd, *J* 11.6 and *J* 5.3); δ_C(75.4 MHz; $CDCl_3$) 155.5 (C), 152.8 (C), 139.8 (C), 136.0 (C), 135.7 (C), 129.3 (CH), 129.0 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 127.2 (CH), 67.7 (CH_2), 55.8 (CH_2), 50.9 (CH); HRMS (ESI+): Calcd for $C_{23}H_{20}N_2O_2Cl$ [M+H]+: 391.1213; Found: 391.1216.

1-(3-(4-Fluorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-ethanone (4k). Reaction time: 18 h; white solid (104.8 mg, 74%); R_f 0.18 (Petroleum ether/EtOAc: 3/1); mp 116–117 °C; IR (KBr) ν_{max}/cm^{-1} 1651, 1604, 1512, 1453, 1410, 1361, 1312, 1231, 1156, 955, 841, 700, 520; δ_H(300 MHz; $CDCl_3$) 7.65–7.61 (2 H, m), 7.34–7.15 (5 H, m), 7.01–6.93 (2 H, m); 4.68 (1 H, dd, *J* 11.6 and *J* 5.2), 4.39 (1 H, dd, *J* 11.7 and *J* 12.2), 4.02 (1 H, dd, *J* 12.2 and *J* 5.1), 2.47 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 169.4 (C), 163.7 (C, *J* 250.1), 155.8 (C), 140.2 (C), 129.5 (CH), 129.3 (CH, *J* 8.4), 127.8 (CH), 127.3 (CH), 127.1 (C, *J* 3.3), 127.0 (CH), 115.6 (CH, *J* 21.8), 54.3 (CH_2), 50.9 (CH), 21.7 (CH_3); HRMS (ESI+): Calcd for $C_{17}H_{16}N_2OF$ [M+H]+: 283.1247; Found: 283.1240.

Benzyl 3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (4l). Reaction time: 19 h; white solid (146.4 mg, 78%); R_f 0.4 (Petroleum ether/EtOAc: 3/1); mp 122–123 °C; IR (KBr) ν_{max}/cm^{-1} 1718, 1603, 1514, 1447, 1417, 1403, 1371, 1302, 1229, 1159, 1128, 979, 857, 695; δ_H(300 MHz; $CDCl_3$) 7.66–7.64 (2 H, m), 7.44–7.16 (10 H, m), 6.98–6.90 (2 H, m), 5.3 (2 H, s), 4.67 (1 H, dd, *J* 11.6 and *J* 5.3), 4.38 (1 H, dd, *J* 11.3 and *J* 11.5), 3.97 (1 H, dd, *J* 11.3 and *J* 5.1); δ_C(75.4 MHz; $CDCl_3$) 163.6.2 (C, *J* 249.3), 155.7 (C), 153.0 (C), 139.9 (C), 136.2 (C), 129.5 (CH, *J* 8.3), 129.4 (CH), 128.6 (CH), 128.38 (CH), 128.35 (CH), 127.8 (CH), 127.3 (CH), 126.9 (C, *J* 3.9), 115.6 (CH, *J* 21.8), 67.8 (CH_2), 64.6 (CH), 55.8 (CH_2), 51.3 (CH); HRMS (ESI+): Calcd for $C_{23}H_{20}N_2O_2F$ [M+H]+: 375.1509; Found: 375.1494.

1-(3,4-Bis(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (4m). Reaction time: 20 h; pale yellow solid (113.8 mg, 70%); R_f 0.12 (Petroleum ether/EtOAc: 2/1); mp 58–60 °C; IR (KBr) ν_{max}/cm^{-1} 1625, 1515, 1466, 1424, 1368, 1325, 1304, 1250, 1173, 1112, 1034, 977, 838; δ_H(300 MHz; $CDCl_3$) 7.61–7.56 (2 H, m), 7.09–7.04 (2 H, m), 6.83–6.76 (4 H, m); 4.61 (1 H, dd, *J* 11.5 and *J* 5.1), 4.31 (1 H, dd, *J* 11.8 and *J* 11.5), 3.95 (1 H, dd, *J* 12.0 and *J* 5.1), 3.76 (3 H, s); 3.75 (3 H, s); 2.44 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 169.3 (C), 160.9 (C), 158.9 (C), 156.9 (C), 132.7 (C), 128.9 (CH), 128.4 (CH), 123.4 (C), 114.7 (CH), 114.0 (CH), 55.38 (CH_3), 55.34 (CH_3), 54.2 (CH_2), 50.2 (CH), 21.6 (CH_3); HRMS (ESI+): Calcd for $C_{19}H_{21}N_2O_3$ [M+H]+: 325.1552; Found: 325.1545.

1-(4-Phenyl-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (4n). Reaction time: 19 h; pale yellow solid (96.4 mg, 71%); R_f 0.28 (Petroleum ether/EtOAc: 2/1); mp 164–166 °C; IR (KBr) ν_{max}/cm^{-1} 1651, 1454, 1416, 1231, 1159, 1089, 1032, 955, 847, 734, 705; δ_H(300 MHz; $CDCl_3$) 7.20–7.36 (6 H, m), 6.92 (1 H, dd, *J* 3.6 and *J* 1.1), 6.88 (1 H, dd, *J* 5.0 and *J* 3.7), 4.63 (1 H, dd, *J* 11.8 and *J* 6.0), 4.41 (1 H, t, *J* 11.8), 4.00 (1 H, dd, *J* 11.8 and *J* 6.0), 2.44 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 169.3 (C), 152.7 (C), 140.2 (C), 134.5 (C), 129.4 (CH), 129.3 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 54.4 (CH_2), 52.0 (CH), 21.6 (CH_3); HRMS (ESI+): Calcd for $C_{15}H_{15}N_2OS$ [M+H]+: 271.0905; Found: 271.0906.

***N*,4-Diphenyl-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide (4o).** Reaction time: 19 h; white solid (130.5 mg, 75%); R_f 0.62 (Petroleum ether/EtOAc: 1/1); mp 154–155 °C; IR (KBr) ν_{max}/cm^{-1} 3389, 1681, 1593, 1531, 1445, 1377, 1310, 1223, 1144, 1100, 1076, 845, 751, 702; δ_H(300 MHz; $CDCl_3$) 8.08 (1 H, s), 7.60–7.58 (2 H, m), 7.38–7.27 (8 H, m), 7.09 (1 H, t, *J* 7.3), 6.98 (1 H, dd, *J* 3.7 and *J* 1.1), 6.91 (1 H, dd, *J* 4.9 and *J* 3.7), 4.70 (1 H, dd, *J* 11.7 and *J* 6.0), 4.48 (1 H, dd, *J* 11.4 and *J* 11.7), 4.09 (1 H, dd, *J* 11.3 and *J* 6.0); δ_C(75.4 MHz; $CDCl_3$) 151.9 (C), 150.8 (C), 140.1 (C), 138.5 (C), 134.3 (C), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 123.1 (CH), 119.1 (CH), 54.7 (CH_2), 52.5 (CH); HRMS (ESI+): Calcd for $C_{20}H_{18}N_3OS$ [M+H]+: 348.1171; Found: 348.1166.

1-(4-Methyl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (4p)[20]. Reaction time: 20 h; pale yellow solid (66.1 mg, 65%); R_f 0.16 (Petroleum ether/EtOAc: 1/1); mp 53–54 °C; IR (KBr) ν_{max}/cm^{-1} 1660, 1586, 1562, 1442, 1357, 1157, 1087, 1030, 992, 953, 834, 780, 762, 702, 688; δ_H(300 MHz; $CDCl_3$) 7.75–7.72 (2 H, m), 7.43–7.41 (3 H, m), 4.11–4.04 (1 H, m), 3.81 (1 H, dd, *J* 11.8 and *J* 4.5), 3.74–3.62 (1 H, m), 2.39 (3 H, s), 1.29 (3 H, d, *J* 7.1); δ_C(75.4 MHz; $CDCl_3$) 169.5 (C), 159.9 (C), 130.6 (C), 130.1 (CH), 128.8 (CH), 126.9 (CH), 52.2 (CH_2), 38.8 (CH), 21.4 (CH_3), 19.0 (CH_3); HRMS (ESI+): Calcd for $C_{12}H_{15}N_2O$ [M+H]+: 203.1184; Found: 203.1176.

(3-Isopropyl-4-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)-methanone (4q). Reaction time: 18 h; colorless oil (110.0 mg, 75%); R_f 0.26 (Petroleum ether/EtOAc: 1/1); IR (KBr) ν_{max}/cm^{-1} 2968, 1694, 1633, 1574, 1494, 1452, 1346, 1249, 1030, 897, 821, 757, 704, 669; δ_H(300 MHz; $CDCl_3$) 8.03 (2 H, d, *J* 6.9), 7.48–7.17 (8 H, m), 4.51 (1 H, dd, *J* 11.4 and *J* 11.9), 4.28 (1 H, dd, *J* 11.3 and *J* 6.0), 4.13 (1 H, dd, *J* 11.9 and *J* 6.2), 2.46–2.37 (1 H, m), 1.10 (3 H, d, *J* 6.7), 1.06 (3 H, d, *J* 7.1); δ_C(75.4 MHz; $CDCl_3$) 167.3 (C), 166.5 (C), 155.2 (C), 139.8 (C), 134.3 (C), 130.9 (CH), 130.2 (CH), 129.3 (CH), 127.8 (CH), 127.6 (CH), 54.5 (CH_2), 51.1 (CH), 28.2 (CH), 20.5 (CH_3), 19.5 (CH_3); HRMS (ESI+): Calcd for $C_{19}H_{21}N_2O$ [M+H]+: 293.1654; Found: 293.1646. Remark: this compound tends to decompose if standing at room temperature.

3-Isopropyl-*N*,4-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (4r). Reaction time: 17 h; pale yellow solid (123.2 mg, 80%); R_f 0.31 (Petroleum ether/EtOAc: 1/1); mp 105–106 °C; IR (KBr) ν_{max}/cm^{-1} 3391, 2973, 2879, 1681, 1590, 1526, 1447, 1388, 1333, 1210, 1139, 1116, 1076, 797, 753, 709, 691, 579; δ_H(300 MHz; $CDCl_3$) 8.04 (1 H, s), 7.54 (2 H, d, *J* 7.7), 7.37–7.25 (5 H, m), 7.18 (2 H, d, *J* 7.1), 7.04 (1 H, t, *J* 7.1), 4.32 (2 H, br s), 3.99 (1 H, br s), 2.46–2.37 (1 H, m), 1.15 (3 H, d, *J* 6.8), 1.08 (3 H, d, *J* 7.0); δ_C(75.4 MHz; $CDCl_3$) 164.4 (C), 152.4 (C), 139.8 (C), 138.8 (C), 129.2 (CH), 129.0 (CH), 127.8 (CH), 127.7 (CH), 122.8 (CH), 119.0 (CH), 53.5 (CH_2), 52.8 (CH), 28.1 (CH), 20.6 (CH_3), 19.6 (CH_3); HRMS (ESI+): Calcd for $C_{19}H_{22}N_3O$ [M+H]+: 308.1763; Found: 308.1758.

General procedure for the transprotection reaction. A solution of pyrazoline **4d** (89.1 mg, 0.25 mmol) in THF (2 ml) was hydrogenated in the presence of Pd/C 10% (10 mg) at 1 atm for 1 h. Then, hydrogen was removed by bubbling the nitrogen through the solution. Triethylamine (0.07 mL, 0.5 mmol, 2 equiv) and *para*-toluenesulfonic anhydride (81.6 mg, 1 equiv) was added at room temperature. The mixture was stirred for 1 h and the

catalyst was removed by filtration (Celite®, CH_2Cl_2).The filtrate was concentrated. Purification by flash chromatography gave pyrazoline **4f** as described in the following characterizations data.

3,4-Diphenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (4f). Pale yellow solid (84.9 mg, 90%); R_f 0.58 (Petroleum ether/EtOAc: 1/1); mp 168–169 °C; IR (KBr) ν_{max}/cm^{-1} 1597, 1493, 1446, 1360, 1166, 1094, 1027, 755, 671, 597, 548; δ_H(300 MHz; $CDCl_3$) 7.85 (2 H, d, *J* 8.1), 7.60–7.57 (2 H, m), 7.34–7.21 (8 H, m), 7.01–6.98 (2 H, m), 4.50 (1 H, dd, *J* 10.5 and *J* 4.9), 3.86 (1 H, t, *J* 10.3), 3.77 (1 H, dd, *J* 10.0 and *J* 4.9), 2.43 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 159.5 (C), 144.6 (C), 139.0 (C), 131.1 (C), 130.3 (CH), 130.2 (C), 129.7 (CH), 129.3 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 58.0 (CH_2), 51.9 (CH), 21.7 (CH_3); HRMS (ESI+): Calcd for $C_{22}H_{21}N_2O_2S$ [M+H]+: 377.1324; Found: 377.1312.

1-(Methylsulfonyl)-3,4-diphenyl-4,5-dihydro-1*H*-pyrazole (4s). White solid (64.0 mg, 85%); R_f 0.50 (Petroleum ether/EtOAc: 1/1); mp 170–171 °C; IR (KBr) ν_{max}/cm^{-1} 1495, 1446, 1340, 1158, 1093, 1015, 961, 840, 784, 767, 753, 697, 590, 552; δ_H(300 MHz; $CDCl_3$) 7.69–7.66 (2 H, m), 7.34–7.23 (8 H, m), 4.73 (1 H, dd, *J* 10.5 and *J* 4.3), 4.14 (1 H, dd, *J* 10.3 and *J* 10.0), 3.91 (1 H, dd, *J* 10.0 and *J* 4.2), 3.15 (3 H, s); δ_C(75.4 MHz; $CDCl_3$) 160.1 (C), 138.6 (C), 130.6 (CH), 130.0 (C), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 56.6 (CH_2), 52.1 (CH), 35.9 (CH_3); HRMS (ESI+): Calcd for $C_{16}H_{17}N_2O_2S$ [M+H]+: 301.1011; Found: 301.1000.

***N*-Cyclohexyl-3,4-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (4t).** Pale yellow solid (80.0 mg, 92%); R_f 0.45 (Petroleum ether/EtOAc: 1/1); mp 160–161 °C; IR (KBr) ν_{max}/cm^{-1} 3384, 2934, 2852, 1651, 1526, 1395, 1130, 691; δ_H(300 MHz; $CDCl_3$) 7.63–7.60 (2 H, m), 7.30–7.18 (8 H, m), 6.03 (1 H, d, *J* 8.3), 4.66 (1 H, dd, *J* 11.6 and *J* 5.3), 4.32 (1 H, dd, *J* 11.5 and *J* 11.3), 4.01 (1 H, dd, *J* 11.1 and *J* 5.0), 3.80–3.70 (1 H, m), 2.10–1.95 (2 H, m), 1.83–1.57 (3 H, m), 1.50–1.16 (5 H, m); δ_C(75.4 MHz; $CDCl_3$) 154.5 (C), 153.9 (C), 140.5 (C), 131.0 (C), 129.4 (CH), 129.2 (CH), 128.5 (CH), 127.5 (CH), 127.4 (CH), 126.9 (CH), 54.8 (CH_2), 51.0 (CH), 48.9 (CH), 34.0 (CH_2), 33.9 (CH_2), 25.7 (CH_2), 25.16 (CH_2), 25.13 (CH_2); HRMS (ESI+): Calcd for $C_{22}H_{26}N_3O$ [M+H]+: 348.2076; Found: 348.2079.

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