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Graphical Abstract

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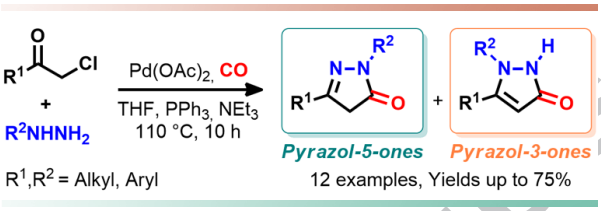

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Palladium-Catalyzed Carbonylative Coupling of α-Chloroketones with Hydrazines: a Simple Route to Pyrazolone Derivatives

Martina Capua, Catia Granito, Serena Perrone,* Antonio Salomone,* and Luigino Troisi

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ABSTRACT

A range of pyrazol-5-one and pyrazol-3-one derivatives has been synthesized in a single step via a palladium-catalyzed carbonylation of aromatic or aliphatic α-chloroketones, in the presence of aromatic or aliphatic hydrazines. A reaction mechanism, explaining the observed regioselectivity, has been also discussed.

1. Introduction

The synthesis of nitrogen-containing heterocycles has always represented an attractive and demanding work for chemists as these moieties have found extensive applications in several fields such as materials science,[1] analytical methods,[2] and most importantly in medicinal chemistry.[3]

Among *N*-heterocycles, pyrazolone rings belong to a very well-studied class of molecules because of their many potential applications such as metal-ions sensors,[4] voltage-sensitive dyes[5] or agrochemicals.[6] Moreover, recent biological studies suggest that the pyrazolone core can be considered an important pharmacophore. Indeed, many pyrazolone derivatives exhibit widespread pharmacological properties, such as anticancer,[7a] analgesic,[7b] antioxidant[7c] or anti-inflammatory[7d] activities (Figure 1).

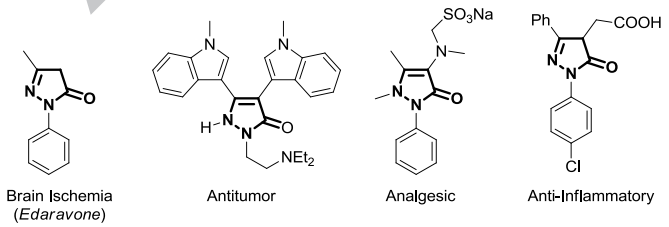

Figure 1. Examples of pyrazolone derivatives exhibiting remarkable biological activities.

An emblematic case is represented by *Edaravone* (Figure 1), developed as a promising drug for brain ischemia and, as recently reported, also for the treatment of myocardial ischemia.[8]

The almost unique strategy employed for the synthesis of pyrazolone derivatives involves the cyclization of β-ketoesters with hydrazines,[9] by the well-known Knorr pyrazole synthesis. Alternative synthetic routes such as the reactions of monosubstituted hydrazines with β-ketoamides,[10] *N*-hydroxy-β-ketoamides,[11] β-ketothioesters[12] or acrylates are less far studied.[13]

In our previous studies we described the Pd-catalyzed carbonylation of allyl- and benzyl halides as a key reaction for the synthesis of a number of carbonyl-containing molecules such as β-lactams,[14a-c] imides,[14d] esters,[14e] amides[14f] or acetylenic ketones.[14g]

More recently we have found that the carbonylation of functionalized halides such as α-chloroketones and α-chloroimines, in appropriate experimental conditions, led to the formation of valuable products such as 2-pyranones,[15a] uracil analogues,[15b] α-alkylidene-β-oxoamides[15c] or β-enaminoacid derivatives.[15d] In all cases a bifunctional compound, namely a β-oxo- or a β-imino-acylpalladium complex, was postulated to be the key intermediate.

It is noteworthy to mention the formation of uracil analogues when α-chloroketones are carbonylated in the presence of *N*,*N*′-disubstituted ureas (Scheme 1).[15b]

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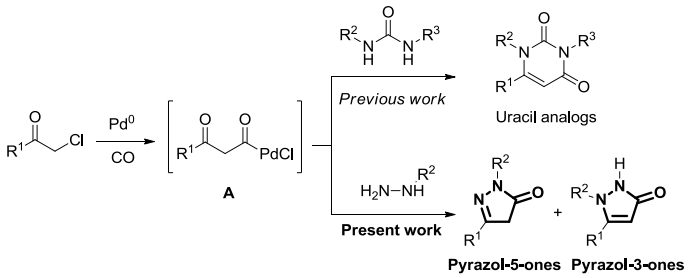


Scheme 1. *β*-oxoacylpalladium species in the synthesis of *N*-heterocycles.

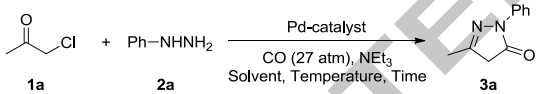
The formation of the pyrimidine-2,4-dione ring can be ascribed to a cyclization reaction between the bifunctional *β*-oxoacylapalladium complex **A** and the urea derivative acting as a 1,3-bidentate nucleophile (Scheme 1). Moreover, it is interesting to note that the proposed mechanistic hypothesis highlights the role of **A** as a synthetic equivalent of a *β*-ketoester, a useful intermediate for the synthesis of heterocycles when coupled with bifunctional nucleophiles.[16]

In this work we describe how this approach can be extended to the synthesis of pyrazolone derivatives by means of carbonylation reaction of *α*-chloroketones in the presence of hydrazines as 1,2-bidentate nucleophiles (Scheme 1).

2. Results and Discussions

Our study commenced by choosing the carbonylative coupling between chloroacetone **1a** and phenylhydrazine **2a** as a model reaction (Table 1).

Table 1. Optimization of the reaction conditions for the model carbonylative coupling between chloroacetone **1a** and phenylhydrazine **2a**.[a]



1a **2a** **3a**

Entry	Pd-Cat.	Temp. (°C)	Time (h)	Solvent	**3a** Yield %[b]
1	$Pd(Ph_3)_4$	110	10	THF	40
2	Pd/C[c]	110	10	THF	33
3	Pd/C[d]	110	10	THF	50
4	$Pd(OAc)_2$	110	10	THF	57
5	$Pd(OAc)_2$	110	10	Toluene	<5
6	$Pd(OAc)_2$	110	10	DMF	14
7	$Pd(OAc)_2$	110	48	THF	10[e]
8	$Pd(OAc)_2$	90	48	THF	41
9	$Pd(OAc)_2$	40	48	THF	17
10	$Pd(OAc)_2$	110	10	THF	71[f]
11	$Pd(OAc)_2$	110	10	THF	72[g]

[a] Reagents and conditions on 1 mmol scale: chloroacetone **1a** (1.0 mmol), phenylhydrazine (1.0 mmol), NEt_3 (4.0 mmol), Pd-catalyst (5 mol%), CO (27 atm), dry THF (15 mL), 110 °C. All reactions were run in duplicate. The reactions with $Pd(OAc)_2$ were performed by adding PPh_3 (20 mol%).

[b] Isolated after column-chromatography on silica gel.

[c] Reaction performed with PPh_3 (20 mol%).

[d] Reaction performed with CyJohnPhos (20 mol%) as phosphine.

[e] Reaction performed under 7 atm of CO.

[f] Reaction performed with 2.0 mmol of **1a**.

[g] Reaction performed with 3.0 mmol of **1a**.

Particularly, we selected the following experimental conditions: chloroacetone **1a** (1.0 equiv), phenylhydrazine **2a** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol %), and NEt_3 (4.0 equiv) were dissolved in dry THF and the resulting solution placed in an autoclave under CO pressure (27 atm). The reaction mixture was then heated at 110 °C under magnetic stirring.

After 10 hours, the first experiment catalyzed by $Pd(PPh_3)_4$ produced the expected pyrazolone **3a**[17] in an encouraging 40% yield (Table 1, entry 1). We then began the optimization studies by testing a series of Pd-catalysts and found that the catalytic system $Pd(OAc)_2/PPh_3$, was the most advantageous, leading to the formation of **3a** in 57% yield (Table 1, entries 2-4).

A brief screening of solvent polarity, reaction times, temperature and CO pressure suggested that THF, 110 °C and 27 atm of carbon monoxide were necessary for a better formation of the target product **3a** in a reasonable reaction time (Table 1, entries 5-9).

Based on our previous studies in the field of Pd-catalyzed carbonylations, we decided to increase the equivalents of the *α*-chloroketone in order to avoid the effects of its dehalogenation reaction.[15a] By using 2.0 equiv of chloroacetone **1a** we were pleased to find that the pyrazolone derivative **3a** could be isolated in 71% yield (Table 1, entry 10). A further increase of **1a** amount (3.0 equiv, Table 1, entry 11) did not affect significantly the **3a** yield (72%).

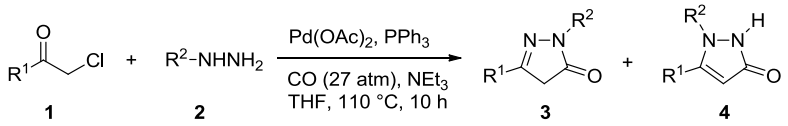
Using the optimized reaction conditions (Table 1, entry 10) we next examined a range of aliphatic and aromatic chloromethyl ketones **1b-i** to access variously substituted pyrazolone derivatives (Table 2). The carbonylative coupling between chloropinacolone **1b** and phenylhydrazine **2a** was successful providing the expected products **3b** in 75 % yield (Table 2, entry 1). When chloroketone **1b** was carbonylated in the presence of *para*-chlorophenylhydrazine **2b**, the reaction afforded two *N*-heterocyclic products; the expected pyrazol-5-one **3c** (55% yield, Table 2, entry 2) along with a small amount of the isomeric pyrazol-3-one derivative **4a** (12% yield, Table 2, entry 2). Despite the low regioselectivity of this reaction, it is important to note that it would be very difficult to get the isomer **4a** through the classic Knorr condensation.

In contrast, the reaction showed to be efficient and regioselective when sterically demanding substrates where employed. Particularly, chloropinacolone **1b** was carbonylated in the presence of *tert*-butylhydrazine **2c** providing the pyrazol-5-one **3d** as a sole regioisomer in 55% yield (Table 2, entry 3).

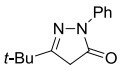
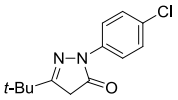
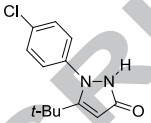
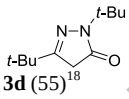
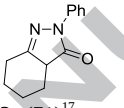
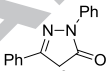
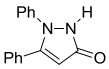
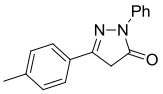
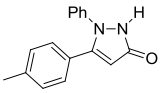
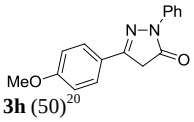
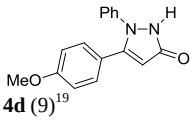
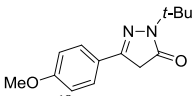
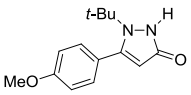
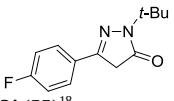
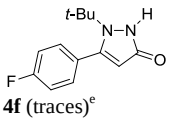
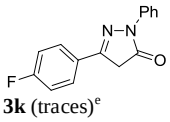
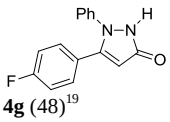
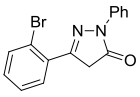
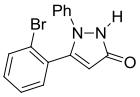
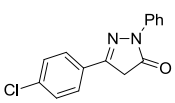
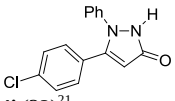
A further experiment suggested that the reaction is effective also with cyclic *α*-chloroketones like **1c**, that was efficiently coupled with phenylhydrazine **2a**; indeed, the target bicyclic compound **3e** was isolated in 71% yield as exclusive isomer (Table 1 , entry 4).

Aromatic ketones were then tested; in a first carbonylation reaction, under the optimized conditions (Table 1, entry 10), *α*-chloroacetophenone **1d** and phenylhydrazine **2a** were coupled to give the diphenyl derivative **3f** in a poor yield (34%, Table 2, entry 5). However, a slight improvement of the reaction efficiency was achieved by increasing the amount of the starting chloroketone **1d** from 2.0 to 3.0 equivalents (55% yield, Table 2, entry 5). Presumably, the dechlorination pathway is more pronounced for aromatic ketones. Furthermore, a small amount of isomeric pyrazol-3-one derivative **4b** (8% yield, Table 2, entry 5) was also isolated after column chromatography.

Table 2. Synthesis of pyrazol-5-one derivatives **3b-m** and pyrazol-3-one derivatives **4a-i**.[a]



1 **2** **3** **4**

entry	α-chloroketone **1**	R^1	hydrazine **2**	R^2	Pyrazol-5-one **3** (Yield %)[c]	Pyrazol-3-one **4** (Yield %)[b]
1	**1b**	*t*-Bu	**2a**	Ph	 **3b** (75)[18]	–
2	**1b**	*t*-Bu	**2b**	4-ClC_6H_4	 **3c** (55)	 **4a** (12)
3	**1b**	*t*-Bu	**2c**	*t*-Bu	 **3d** (55)[18]	–
4	**1c**[c]		**2a**	Ph	 **3e** (71)[17]	–
5	**1d**	Ph	**2a**	Ph	 **3f** (55)[d,17]	 **4b** (8)[19]
6	**1e**	*p*-MeC_6H_4	**2a**	Ph	 **3g** (55)	 **4c** (7)[19]
7	**1f**	*p*-$MeOC_6H_4$	**2a**	Ph	 **3h** (50)[20]	 **4d** (9)[19]
8	**1f**	*p*-$MeOC_6H_4$	**2c**	*t*-Bu	 **3i** (68)[18]	 **4e** (traces)[e]
9	**1g**	*p*-FC_6H_4	**2c**	*t*-Bu	 **3j** (55)[18]	 **4f** (traces)[e]
10	**1g**	*p*-FC_6H_4	**2a**	Ph	 **3k** (traces)[e]	 **4g** (48)[19]
11	**1h**	*o*-BrC_6H_4	**2a**	Ph	 **3l** (traces)[e]	 **4h** (45)
12	**1i**	*p*-ClC_6H_4	**2a**	Ph	 **3m** (21)	 **4i** (32)[21]

[a] Reagents and conditions on 1.0 mmol scale: hydrazine **2** (1.0 mmol), chloroketone **1** (2.0 mmol for aliphatic ketones **1b-c** or 3.0 mmol for aromatic ketones **1d-i**), NEt_3 (4.0 mmol), Pd-catalyst (5 mol%), PPh_3 (20 mol%), CO (27 atm), dry THF (15 mL), 110 °C for 10 hours. For the experimental procedures, see Ref. 22

[b] Isolated after column-chromatography on silica gel.

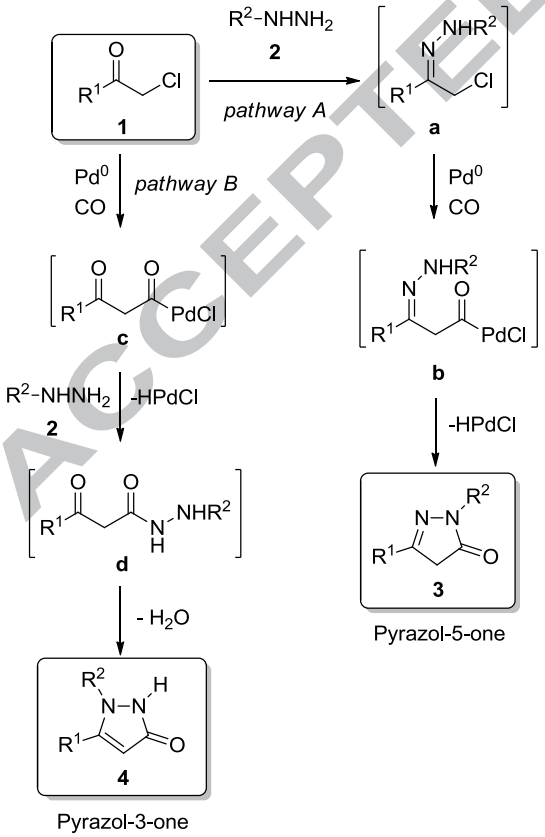
[c] The structure showed in the column R^1 is intended to be as the whole chloroketone and not a substituent.

[d] Product **3f** was isolated in 34% yield when 2.0 mmol of chloroacetophenone **1d** were used.

[e] Detected by GC-MS analysis on the crude reaction mixture.

The electronic nature of the aromatic ketone was also varied. The presence of an electron donating group on the phenyl ring was well tolerated by the methodology; specifically, when the phenylhydrazine **2a** reacted with *para*-methyl and *para*-methoxy acetophenones **1e** and **1f** our method afforded the desired products **3g** and **3h** in a moderate yield and in a good regioselectivity (Table 2, entries 6-7). Only negligible amounts of **4c** and **4d** derivatives (7% and 9% yield, respectively) were detected in the crude reaction mixture and isolated by column chromatography (Table 2, entries 6-7).

On the other hand, when aromatic ketone **1f** has been subjected to the carbonylative coupling with aliphatic hydrazine **2c**, the pyrazol-5-one derivative **3i** was isolated in a satisfactory yield (68%, Table 2, entry 8) and just a trace amount of the isomeric pyrazol-3-one **4e** was detected by GC-MS analysis on the crude mixture. The influence of an electron withdrawing group on the phenyl ring of acetophenone derivatives **1** has been also checked. The reaction of fluorinated ketone **1g** with *tert*-butylhydrazine **2c** smoothly afforded the product **3j** (55% yield, Table 2, entry 9) together with traces (<5%) of the pyrazol-3-one **4f**. Surprisingly, the same ketone **1g** gave an opposite regioselectivity in the reaction with the aromatic hydrazine **2a**: the expected product **3k** was just detected by GC-MS analysis in the crude reaction mixture and only the pyrazol-3-one derivative **4g** has been isolated in 48% yield after column chromatography (Table 2, entry 10). A similar trend was also observed in the reaction of **2a** with *ortho*-bromo substituted ketone **1h**. In fact, the method afforded the product **4h** in a moderate yield and as a sole regioisomer (45% yield, Table 2, entry 11). An inversion of regioselectivity has been also found in the carbonylation of *para*-chloro derivative **1i** in the presence of the hydrazine **2a**. Specifically, a separable 2:3 mixture of isomers **3m** and **4i** was formed in 54% total yield (Table 2, entry 12).



Scheme 2. Proposed mechanism for the formation of pyrazol-5-one **3** and pyrazol-3-one **4** via acylpalladium intermediates **b**, **c**.

The formation of the observed isomeric pyrazolone derivatives **3** and **4** can be rationalized on the basis of a simplified reaction mechanism as follows: two possible pathways (*A* or *B*, Scheme 2) can be considered operative when α-chloroketones are carbonylated in the presence of hydrazines. The *pathway A* involves the initial formation of the α-chlorohydrazone **a** followed by a Pd-catalyzed carbonylation to afford the acylpalladium complex **b.** The intramolecular *N*-acylation should then produce the pyrazol-5-one compound **3**. The *pathway B* starts with the carbonylation of the α-chloroketone **1** to afford an acylpalladium complex **c.** The latter acylates the hydrazine **2** to give the intermediate **d** that, after an intramolecular condensation, produces the isomeric pyrazol-3-one **4**. Therefore, the regioselectivity observed in each experiment (Table 2) should be dependent by the relative rate of two synthetic processes depicted as *pathways A* and *B* in Scheme 2.

In conclusion, our work opens a new synthetic access to a range of pyrazol-5-one and pyrazol-3-one derivatives by means of Pd-catalyzed carbonylation of α-chloroketones in the presence of hydrazines. Although different synthetic methods for the preparation of pyrazolones are today available, they often involve harsh reaction conditions such as the use of strong acids.[9] Our approach, instead, represents a smooth way to the synthesis of pyrazolones in mild reaction conditions. Efforts to extend the employment of acylpalladium intermediates to the synthesis of other *N*-and *O*-heterocyclic systems are currently underway in our laboratory.

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22 *General procedure for the synthesis of pyrazolones* **3a-m** *and* **4a-i**: a solution containing the *α*-chloroketone **1** (2.0 mmol or 3.0 mmol in the case of aromatic ketones), hydrazine **2** (1.0 mmol), $Pd(AcO)_2$ (11 mg, 5 mol%), PPh_3 (52 mg, 0.20 mmol), and NEt_3 (0.5 mL, 4.0 mmol) in anhydrous THF (15 mL) was placed in a 45 mL autoclave. The autoclave was purged, pressurized with CO (27 atm), and then heated at 110 °C under magnetic stirring, for 10 h. After this time, the solution was cooled to room temperature, and the solvent was removed under reduced pressure. The crude reaction mixture was then purified by chromatography on silica gel [petroleum ether/AcOEt (90:10 to 30:70)] to obtain the corresponding pyrazolones derivatives **3a-m** and **4a-i** as pure compounds.
Compounds **3a**, **3b**, **3d**, **3e**, **3f**, **3h**, **3i**, **3j** and **4b**, **4c**, **4d**, **4g**, **4i** are known and their characterization data are in agreement with those reported in the literature (see references 17–21 cited in Table 2).
Characterization data for compounds **3c**,**g**,**m** and **4a**,**h** are unknown and given below:

3-(tert-Butyl)-1-(4-chlorophenyl)-1H-pyrazol-5(4H)-one (**3c**). Pale yellow oil (138 mg, 55%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.27 (9 H, s), 3.45 (2 H, s), 7.47 (2 H, d, J = 7.5 Hz), 7.59 (2 H, d, J = 7.5 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 28.1, 37.4, 38.9, 128.4, 129.0, 132.9, 136.2, 164.5, 171.1 ppm. GC/MS (70 eV): *m/z* (%) = 250 (100) $[M]^+$, 235 (95), 207 (10), 111 (48), 83 (61). HRMS (ESI): calcd. for $C_{13}H_{16}ClN_2O$ $[M+H]^+$ 251.0951; found 251.0953.

1-Phenyl-3-(p-tolyl)-1H-pyrazol-5(4H)-one (**3g**). Brown solid (138 mg, 55%), m.p. 150-152 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.39 (3 H, s), 3.76 (2 H, s), 7.18-7.24 (3 H, m), 7.40-7.43 (2 H, m), 7.63 (2 H, d, J = 7.3 Hz), 7.97 (2 H, m) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.5, 39.6, 118.9, 125.1, 125.9, 128.1, 128.8, 129.5, 138.1, 141.1, 154.7, 170.2 ppm. GC/MS (70 eV): *m/z* (%) = 250 (100) $[M]^+$, 208 (15), 117 (78), 91 (47). HRMS (ESI): calcd. for $C_{16}H_{15}N_2O$ $[M+H]^+$ 251.1184; found 251.1187.

3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-5(4H)-one (**3m**). Yellow solid (57 mg, 21%), m.p. 146-148 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.83 (2 H, s), 7.42-7.46 (5 H, m), 7.70-7.73 (2 H, m), 7.95 (2 H, d, J = 7.7 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 39.5, 119.1, 127.2, 128.9, 129.0, 129.2, 129.3, 136.7, 137.9, 153.5, 170.0 ppm. GC/MS (70 eV): *m/z* (%) = 270 (100) $[M]^+$, 228 (13), 137 (45), 91 (53), 77 (51). HRMS (ESI): calcd. for $C_{15}H_{12}ClN_2O$ $[M+H]^+$ 271.0638; found 271.0636.

5-(tert-Butyl)-1-(4-chlorophenyl)-1H-pyrazol-3(2H)-one (**4a**). Pale yellow oil (30 mg, 12%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.21 (9 H, s), 5.53 (1 H, s), 7.31 (2 H, d, J = 7.5 Hz), 7.40 (2 H, d, J = 7.5 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 30.6, 40.8, 90.6, 128.2, 129.1, 130.2, 135.1, 161.4, 177.6 ppm. GC/MS (70 eV): *m/z* (%) = 250 (51) $[M]^+$, 235 (100), 200 (33), 111 (25). HRMS (ESI): calcd. for $C_{13}H_{16}ClN_2O$ $[M+H]^+$ 251.0951; found 251.0949.

5-(2-Bromophenyl)-1-phenyl-1H-pyrazol-3(2H)-one (**4h**). Yellow oil (141 mg, 45%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.94 (1 H, s), 7.18-7.30 (8 H, m), 7.57 (1 H, d, J = 7.8 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 95.7, 124.0, 126.9, 127.2, 128.9, 130.5, 132.1, 133.1, 138.9, 142.7, 162.5 ppm. GC/MS (70 eV): *m/z* (%) = 314 (62) $[M]^+$, 235 (34), 207 (100), 180 (30), 103 (23), 77 (51). HRMS (ESI): calcd. for $C_{15}H_{11}BrN_2O$ $[M+H]^+$ 315.0133; found 315.0135.

Highlights

- A Pd-carbonylative coupling of α-chloroketones and hydrazines leads to pyrazolones
- An acylpalladium complex is proposed as a reactive intermediate
- The process offers an alternative to the classical Knorr pyrazole synthesis