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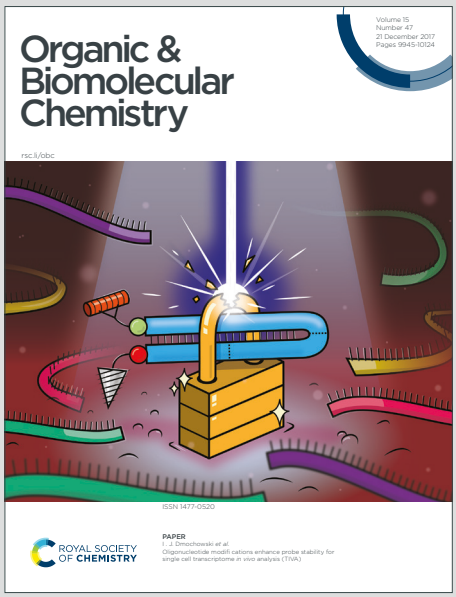

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ARTICLE

Nickel-Catalyzed C3-Acylation of 2*H*-Indazoles with Aldehydes

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A direct coupling of 2*H*-Indazoles' C3 position and acyl groups has been achieved to produce 3-acyl-2*H*-Indazoles. The Ni(II)-catalyzed acylation might proceed through a radical pathway for the reaction of 2*H*-Indazoles with either aryl or alkyl aldehydes at the presence of the free radical initiator TBHP and additive PivOH. This method provided a superior approach to fulfil the direct C3-acylation of 2*H*-indazoles with yields up to 91%. And various substituted 2*H*-Indazoles were well tolerated with this method that enriched the diversity of 2*H*-indazole derivatives. In comparison with previously reported approaches of C3-acylation of 2*H*-indazoles , the developed reaction represented a more convenient and economical method directly using aldehydes to be acylation agents.

Introduction

Indazoles, which are widely distributed in herb seeds, were proved to have potentials in antitumor activity,[1] anti-inflammatory activity,[2] and HIV protease inhibition.[3] Generally, there are two indazole isomers, 1*H*-indazoles and 2*H*-indazoles.[4] Over the past decades, 1*H*-indazoles have represented a kind of important structures in clinical treatments, such as Lonidamine,[5] Granisetron,[6] and Axitinib (Figure 1).[7] Coincidentally, 2*H*-indazoles were also verified of pharmacological activities recently, and the applications of which in pharmaceutical researches and clinical studies have been realized, for instance, Pazopanib and MK-4827 (Figure 1).[8, 9] On the other hand, synthetic routes of 2*H*-indazoles were less prevalent than 1*H*-indazoles, although there were couples of publications reporting syntheses of 2*H*-indazoles.[10] It would be valuable of developing new synthetic approaches to induce different moieties on 2*H*-indazole core for the increase of molecular diversity and for the development of new bioactive compounds.

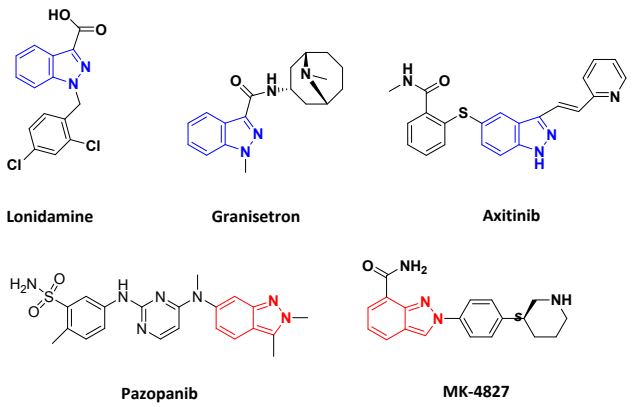
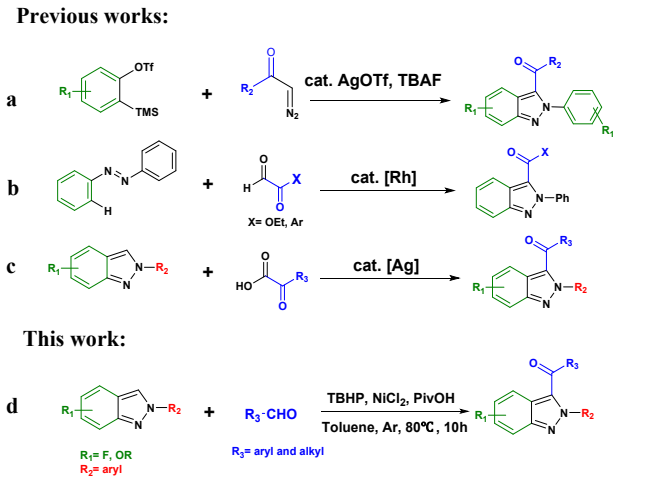


Figure 1. Examples of bioactive indazoles

It was no denying that the C3-acylation may expend the molecular diversity of 2*H*-indazoles. A few studies have been carried out on syntheses of 2*H*-indazoles with a C3-keto substituent. As reported, Wang *et al.* developed the approach for the synthesis of 3-acyl-2*H*-Indazoles using diazocarbonyl reagents and benzynes through silver-catalyzed [3+2]-cycloaddition reaction (Scheme 1, **a**),[11] and Jeong et al. demonstrated the direct C–H functionalization, accompanied by the use of rhodium catalyst, of azobenzenes reacting with ethyl glyoxalate or aryl glyoxals (Scheme 1, **b**).[12] Moreover, Bogonda et al. revealed a direct acyl radical addition to 2*H*-indazole through $AgNO_3$-catalyzed decarboxylative cross-coupling of α-keto acid (Scheme 1, **c**).[13] Obviously, all above reactions need a noble metal participating to be the catalyst.

Herein, we reported a new approach (Scheme 1, **d**) of nickel-catalyzed C3-acylation reaction of 2*H*-indazoles via directly reacting with either aryl or alkyl aldehydes, obtaining



Scheme 1. Synthetic approaches to 3-acyl-2H-Indazoles

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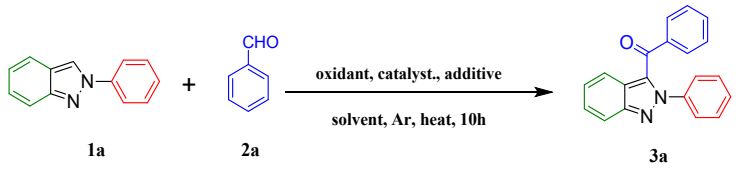
corresponding products in yields of up to 91%. In this work, the preciously-used metal catalyst was replaced by a bivalent nickel catalyst. Meanwhile, aldehydes with extensive commercial sources took the place of hard-won accessed starting material, such as α-keto acids, which required to be particularly synthesized. The developed reaction appeared more convenient and economical method to synthesize 3-acyl-2*H*-indazoles in comparison with previously reported ones.

Results and discussion

Based on forerunner's researches, it was hypothesized that a metallaphotocatalysis protocol could contribute to acylation reactions by a free radical pathway.[14] Additionally, peroxides were frequently applied for a radical initiator in such kind of reactions.[15] Therefore, we developed the method for the acylation at the C3 position of 2*H*-indazoles reacting with an aldehyde in the presence of both oxidant and metal catalyst. Initially, the studies were commenced by investigating the reaction of 2-(2-phenyl)-2*H*-indazole (**1a**) and benzaldehyde (**2a**) using $NiCl_2$, *tert*-butyl hydroperoxide (TBHP), and pivalic acid (PivOH) to be the catalyst, oxidant, and additive, respectively. At first, the reaction solvent was screened. Results indicated that the reaction took place in various solvents, like dioxane, and toluene, to produce **3a** in yields ranging from 33% to 86% at 80 °C (Table 1, entries 1-7), and toluene served as the best solvent for the reaction to get the yield of 86% (Table 1, entry 7).

Next, the role of metal catalyst was put into discussion to evaluate the most efficient one. Since it was reported that palladium salt in combined with TBHP-PivOH catalysed C2-acylation of indoles reacting with aldehydes effectively,[16] it was supposed that the method could also work in the C3-acylation of 2*H*-indazoles, too. As listed in Table 1, $Pd(OAc)_2$ was tested to catalyse the reaction in a yield of 60% in combination with TBHP-PivOH (Table 1, entry 8), showing a lower reaction-promoting efficiency than the catalyst $NiCl_2$ (Table 1, entry 7). Meanwhile, another two nickel catalysts, $Ni(dppp)Cl_2$ (Table 1, entry 9) and $Ni(OAc)_2{\cdot}4H_2O$ (Table 1, entry 10), were individually used to be the catalyst, making the reaction in a yield of 66% and 43%, respectively. Typically, the reaction with $Ni(OAc)_2{\cdot}4H_2O$ obtained the product **3a** in a similar yield of around 40% as to the one without a metal catalyst (Table1, entry 11). By the way, when the usage of $NiCl_2$ reduced to 10% mol, the reaction yield decreased to 71% (Table 1, entry 7[c]).

Table 1. Screening of Reaction Conditions [a]



1a 2a 3a

Entry	Solvent	Catalyst	Oxidant	Additive	Yield (%)[b]
1	MeCN	$NiCl_2$	TBHP	PivOH	72
2	EtOH	$NiCl_2$	TBHP	PivOH	33
3	PhCl	$NiCl_2$	TBHP	PivOH	60
4	PhBr	$NiCl_2$	TBHP	PivOH	54
5	Xyl	$NiCl_2$	TBHP	PivOH	53
6	Diox	$NiCl_2$	TBHP	PivOH	60
7[c]	PhMe	$NiCl_2$	TBHP	PivOH	86
8	PhMe	$Pd(OAc)_2$	TBHP	PivOH	60
9	PhMe	$Ni(dppp)Cl_2$	TBHP	PivOH	66
10	PhMe	$Ni(OAc)_2{\cdot}4H_2O$	TBHP	PivOH	43
11	PhMe	-	TBHP	PivOH	40
12[d]	PhMe	$NiCl_2$	DTBP	-	NR
13	PhMe	$NiCl_2$	BPO	-	23
14	PhMe	$NiCl_2$	$PhI(OAc)_2$	-	11
15	PhMe	$NiCl_2$	TBHP	-	66
16	PhMe	$NiCl_2$	TBHP	$PhB(OH)_2$	18
17	PhMe	$NiCl_2$	TBHP	AcOH	62

[a]Reaction conditions:**1a** (0.26mmol), **2a** (0.78mmol, 3 equiv), oxidant (0.52mmol, 2 equiv), catalyst (20% mol), additive (0.52mmol, 2 equiv), solvent (1mL), under argon environment, 80°C, for 10h. [b]Isolated yields after column chromatography. [c]Reduce the usage of $NiCl_2$ to 10% mol, the yield was 71%. [d]Reacting at 120°C, the yield was 30%. TBHP = *tert*-Butyl hydroperoxide, PivOH = Pivalic acid, Xyl = Xylene, Diox= Dioxane, DTBP = Di-*tert*-butyl peroxide, NR= No reaction, BPO = Dibenzoyl peroxide.

acetonitrile, ethanol, chlorobenzene, bromobenzene, xylene,

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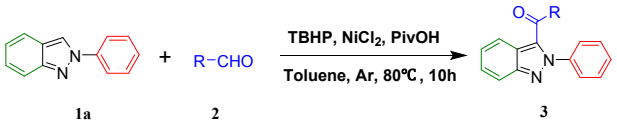
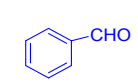
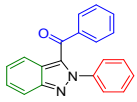
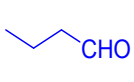
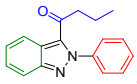
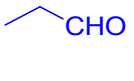
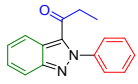
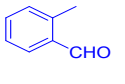
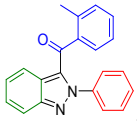
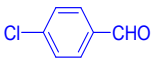
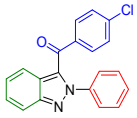
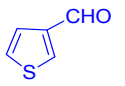
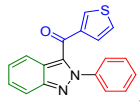
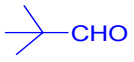
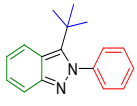
Through above results, further optimizations of the reaction condition were encouraged to focus on various oxidants triggering off the free radical reaction. All the chosen oxidants, including Di-*tert*-butyl peroxide (DTBP), Dibenzoyl peroxide (BPO), $PhI(OAc)_2$, and TBHP (Table 1, entries 12-15), respectively, initiated the C3-acylation reaction of **1a** and **2a** without an additive. Among these reactions, TBHP was the most effective oxidant to produce **3a** in a yield of 66% (Table 1, entry 15). In addition, it was found that the acylation reaction did not take place using DTBP at the temperature of 80°C, while the yield increased to 30% at 120 °C (Table 1, entry 12[d]). The results suggested that the Ni-catalyzed reaction at the C3 position of 2*H*-indazoles with the aldehyde would be elicited by oxyradical, since published data demonstrated that the appropriate excitation temperature for DTBP was 100 to 120 °C.[17] In the meantime, it was noticed that the additive PivOH was also favorable to the acylation reaction by comparing entries 7 (reaction yield, 86%) and 15 (reaction yield, 66%) in Table 1. Furthermore, it was indicated that the reaction yield was also highly sensitive to Lewis acid additives. As illustrated in Table 1, the reaction yields were 18% and 62%, respectively, in the presence of phenyl boric acid (Table 1, entry 16) or acetic acid (Table 1, entry 17) to be the additive. In comparison, PivOH was proved to be the best additive for the Ni-catalyzed C3-acylation reaction (yield, 86%) of 2*H*-indazoles reacting with aldehydes. So far, the studies demonstrated that 2*H*-indazoles C3-acylation reaction condition with the maximum yield of 86% was obtained with toluene as solvent, involving TBHP (0.52mmol, 2 equiv.), anhydrous nickel chloride (20 mol %), and pivalic acid (0.52mmol, 2 equiv.) under the argon atmosphere at 80 °C for 10 hours.

With the optimized reaction condition in hand, we then investigated the scope with various aldehydes. As listed in Table 2, both aryl and alkyl aldehydes can react with compound **1a** to provide corresponding C3-acylated 2*H*-Indazoles in good yields over 50% under above condition. Typically, *n*-butyraldehyde reacted with **1a** to produce **3b** in the highest yield of 91% (Table 2**,** entry 2). Similarly, another alkyl aldehyde propionaldehyde produced **3c** (Table 2**,** entry 3) in a good yield of 71%. Besides, the reaction yields decreased to 74% (product **3d**) and 58% (product **3e**), respectively, when benzaldehyde was replaced by *ortho*-methyl-benzaldehyde (Table 2**,** entry 4) or *para*-chloro-benzaldehyde (Table 2**,** entry 5). Furthermore, heterocyclic thiophene-3-carbaldehyde was also tested to react with compound **1a**, producing **3f** in a relatively low yield of 47% (Table 2**,** entry 6). However, a limitation of current method existed for pivalaldehyde, which did not make acylation but introduced a *tert*-butyl group at the C3-position of compound **1a**, obtaining the product 3-*tert*-butyl-2*H*-indazole **3g** in a yield of 60%. It could be on the reason of the unstability of *tert*-butyl acyl radical, which might go further decarbonylation to a *tert*-butyl radical, participating to the reaction with 2*H*-indazole.[13]

In order to further discuss the applicability of the developed method, various substituted 2*H*-Indazoles and aldehydes were chosen as substrates to produce different 3-acyl-2*H*-indazoles **4a**-**4l** (Scheme 2). Gratifyingly, many substituents, such as fluoro, chloro, methyl, and alcoxy, were well tolerated for the reaction, and electron properties did not show significant effects on the reactivity. Moreover, it was found that aryl aldehydes made the C3-acylation reactions of 2*H*-indazoles in lower yields than alkyl aldehydes, for example, **4a** (76%) *vs* **4c** (86%) and **4b** (64%) *vs* **4d** (85%), likely on the reason of steric hindrance of aryl aldehydes. We also tested the C3-acylation reactions of 2-(pyridin-2-yl)-2*H*-indazole with alkyl and aryl aldehydes to get the C3-acylated 2-(pyridin-2-yl)-2*H*-indazoles

Table 2. Scope of aldehydes in the $NiCl_2$-Catalyzed Radical Addition to 2*H*-Indazole[a]



Entry	Aldehyde	Product	Yield(%)[b]
1		 **,3a**	86
2		 **,3b**	91
3		 **,3c**	71
4		 **,3d**	74
5		 **,3e**	58
6		 **,3f**	47
7		 **,3g**	60

[a]Reaction conditions:**1a** (0.26mmol), **2** (0.78mmol), TBHP (2 equiv), $NiCl_2$ (20%mol), PivOH (2 equiv), Toluene (1mL), under argon atmosphere, 80°C, 10h. [b]Isolated yields after column chromatography.

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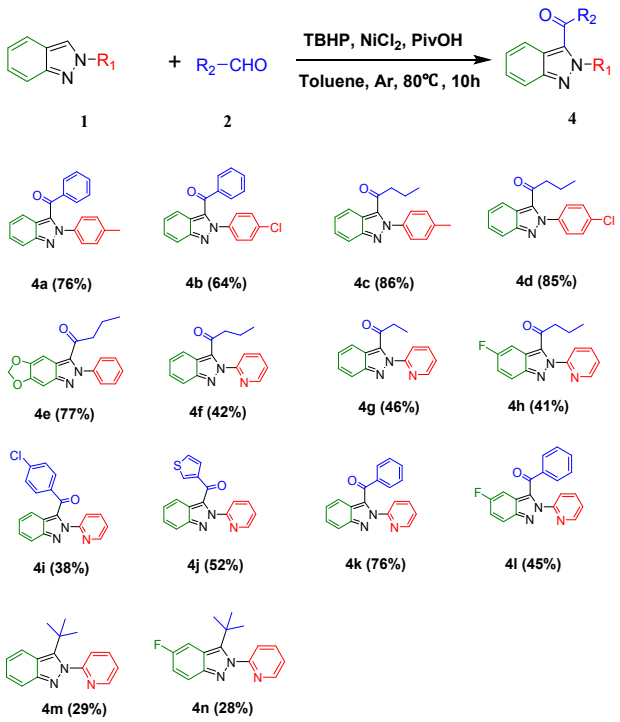
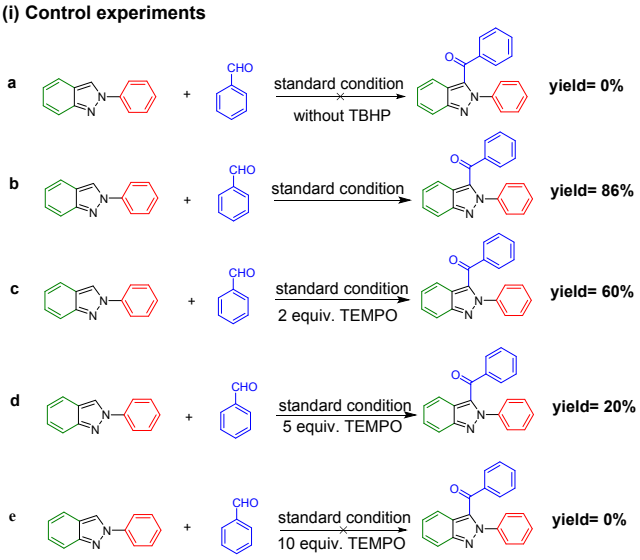


Scheme 2. Substrate scope of 2*H*-indazoles

4f-**4l**. In the mean time, it was also noticed that pivalaldehyde did not make acylation but had a substituent of *tert*-butyl group (products **4m** and **4n**) at the C3-position of 2-(pyridin-2-yl)-2*H*-indazole, either. Similar to the C3-acylation of 2-phenyl-2*H*-indazole, straight chain alkyl aldehydes conducted higher yields than branched alkyl aldehydes, such as **4f** (42%) *vs* **4m** (42%),**4h** (41%) *vs* **4n**(28%), which could also be induced by bigger steric hindrance of branched alkyl group than straight alkyl chain.Considering the wealth of 2*H*-Indazoles accessible, this process represents a powerful and distinct approach toward their construction under mild reaction conditions with readily available starting materials.

To explore the mechanism of nickel-catalyzed C3-acylation of 2*H*-indazoles with aldehydes, we carried out control experiments as illustrated in Scheme 3. As reported in literatures, *tert*-butyl hydroperoxide (TBHP) has been validated to serve as the radical initiator.[18] In fact, our experiments demonstrated that the reaction didn't take place in the absence of TBHP (Scheme 3, **a**). Furthermore, we attempted to capture the radical species with increasing equivalent amount of 2,2,6,6-*tetra*-methylpiperidine-1-oxyl (TEMPO) (Scheme 3, **b**-**e**).[19] It was found that the yield sharply decreased as the equivalent of TEMPO increased. Especially, the addition of 10 equivalent of TEMPO made the reaction failed (Scheme 3, **e**), illustrating the involvement of radical species in the current synthetic route to 3-acyl-2*H*-indazoles. Based on the results of control experiments and previous publications,[20] we proposed a plausible pathway for this reaction. As depicted in Scheme 3, Ni(II) and PivOH might firstly form [Ni(PivO)$_2$]. Then, 2-(2-phenyl)-2*H*-indazole was evolved into a complex **A**, followed by the oxidative addition of carbonyl radical **B** which was excited by TBHP from aldehydes. This process may afford intermediate **C**, and then the product 3-acyl-2*H*-Indazoles was obtained via reductive elimination. At the same time, nickel intermediate **C**



Scheme 3. Proposed mechanism

was converted to a Ni(I) specie. Finally, it was assumed that the Ni(I) species might be converted back to a Ni(II) species, likely through the involvement of THBP or PivOH, to continue the catalytic cycle. We may suppose that the participating nickel catalyst might promote the transfer of electrons to make the reaction more efficient.[20c-e] Not only that, PivOH might favor the formation of nickel complex with 2*H*-indazoles.[20f, g]

Experimental

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General methods. All reagents and solvents were purchased from commercial sources and used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) on Silica gel plates (GF254). The TLC plates were isualized by shortwave (254 nm) or longwave (365 nm) UV light. Column chromatography was carried out using silica gel (200-300 mesh) to purify the product. ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6 on Bruker 500 MHz spectrometers using TMS as the internal standard. Chemical shifts are given in ppm downfield from tetramethylsilane (TMS) as an internal reference, and coupling constants (*J*-values) are in Hertz (Hz). ^{1}H NMR assignment abbreviations are the following; singlet (s), doublet (d), triplet (t), quartet (q), broad singlet (bs), doublet of doublets (dd), triplet of doublets (td), doublet of a triplets (dt) and multiplet (m). The high-resolution mass spectra (HRMS) were recorded in the FAB mode on Agilent 1290 HPLC-6224.

General procedure for the reaction of 2*H*-indazoles with aldehydes: 2-phenyl-2*H*-indazole (50mg, 0.26 mmol), aldehydes (0.78mmol, 3 equiv), TBHP (71 μL, 2 equiv), $NiCl_2$ (6.1 mg, 20%mol), PivOH (53.04 mg, 0.52 mmol) were reacted in Toluene (1mL) under argon atmosphere at 80℃ for 10h. After cooling, the mixture was poured into the EtOAc (5.0 mL) and washed with water (3 × 10.0 mL), brine (3 × 10.0 mL), then dried over MgSO4. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography (Petroleum ether : EtOAc = 10:1) to afford the final product.

Phenyl-(2-phenyl-2*H*-indazol-3-yl)-methanone (3a). Pale yellow solid in a yield of 86% (67 mg). ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[13] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92-7.84 (m, 3H), 7.62-7.58 (m, 1H), 7.55 (t, *J* = 1.90 Hz, 1H), 7.53 (t, 1H), 7.41 (m., 7H), 7.18 (ddd, *J* = 8.62, 6.62, 0.86 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 186.00, 148.60, 140.53, 137.84, 133.59, 132.30, 129.93, 129.10, 128.96, 128.66, 127.06, 125.57, 125.05, 124.10, 120.62, 118.57, 77.37, 77.05, 76.74.

1-(2-Phenyl-2*H*-indazol-3-yl)-butan-1-one (3b). Yellow solid in a yield of 91% (76 mg). ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[13] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 8.40, 1.09 Hz, 1H), 7.89-7.86 (dt, 1H), 7.54-7.51 (m, 3H), 7.48-7.46 (m, 2H), 7.44-7.35 (m, 2H), 2.85 (t, *J* = 8.83, 5.68 Hz, 2H), 1.77-1.69 (m, 2H), 0.94 (t, *J* = 7.41 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.87, 148.49, 141.52, 129.42, 129.05, 126.93, 126.19, 125.91, 122.93, 120.84, 118.97, 77.34, 77.09, 76.83, 44.38, 17.44, 13.79.

1-(2-Phenyl-2*H*-indazol-3-yl)-propan-1-one (3c). Yellow solid in a yield of 71% (51 mg). ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[13] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.42 Hz, 1H), 7.88 (d, *J* = 8.53 Hz, 1H), 7.55-7.52 (m, 3H), 7.49-7.46 (m, 2H), 7.45-7.36 (m, 2H), 2.92 (q, *J* = 7.22 Hz, 2H), 1.18 (t, *J* = 7.22 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 191.21, 148.49, 141.57, 132.80, 129.45, 129.20, 129.05, 126.93, 126.21, 126.11, 125.96, 122.93, 120.89, 119.00, 77.31, 77.06, 76.81, 35.80, 27.05, 7.91.

(2-Phenyl-2*H*-indazol-3-yl)-(*o*-tolyl)-methanone (3d). Milky white solid in a yield of 74% (60 mg). ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[13] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31-8.29 (m, 1H), 7.92 (td, *J* = 8.11, 0.88 Hz, 1H), 7.86-7.82 (m, 2H), 7.40-7.35 (m, 2H), 7.33 (ddd, *J* = 7.37, 3.72, 1.59 Hz, 2H), 7.27-7.20 (m, 3H), 7.16 (q, 1H), 7.08 (t, *J* = 7.52 Hz, 1H), 2.58 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.06, 152.13, 148.99, 148.03, 138.76, 138.59, 138.30, 133.67, 132.74, 131.87, 131.56, 131.46, 129.73, 127.77, 125.82, 125.49, 125.18, 124.08, 123.48, 120.64, 118.51, 118.02, 77.32, 77.06, 76.81, 20.37.

(4-Chlorophenyl)-(2-phenyl-2*H*-indazol-3-yl)-methanone (3e). Yellow solid in a yield of 58% (50 mg). ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[13] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91-7.87 (m, 1H), 7.81-7.78 (m, 2H), 7.52 (td, *J* = 5.64, 2.53, 2H), 7.45-7.40 (m, 5H), 7.40-7.37 (m, 2H), 7.21 (q, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 184.64, 148.64, 140.44, 140.07, 136.19, 131.89, 131.24, 129.13, 129.07, 129.02, 127.12, 125.56, 125.31, 124.07, 120.37, 118.69, 77.27, 77.01, 76.76.

(2-Phenyl-2*H*-indazol-3-yl)-(thiophen-3-yl)methanone (3f). Yellow solid in a yield of 47% (37 mg). ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[13] ^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (d, *J* = 8.76 Hz, 1H), 7.76 (dd, *J* = 4.93, 1.09 Hz, 1H), 7.67-7.61 (m, 2H), 7.59-7.56 (m, 2H), 7.47-7.37 (m, 4H), 7.25-7.20 (m, 1H), 7.12 (dd, *J* = 4.89, 3.85 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.90, 148.63, 144.23, 140.37, 135.47, 135.43, 132.16, 129.16, 128.97, 128.21, 127.99, 127.13, 125.38, 124.83, 123.56, 120.42, 118.47, 77.27, 77.01, 76.76.

3-(*tert*-Butyl)-2-phenyl-2*H*-indazole (3g). Yellow solid in a yield of 60% (39 mg). ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[13] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.92 (m, 1H), 7.67 (td, *J* = 8.73, 0.95 Hz, 1H), 7.51-7.41 (m, 5H), 7.30-7.26 (m, 1H), 7.06-7.03 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.48, 144.45, 142.95, 129.42, 128.50, 128.11, 126.00, 122.64, 120.81, 119.73, 117.84, 77.33, 77.08, 76.82, 34.78, 31.87.

Phenyl-(2-(*p*-tolyl)-2*H*-indazol-3-yl)-methanone (4a). Pale yellow solid in a yield of 76% (62 mg). ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported literature data.[13] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90-7.85 (m, 3H), 7.62-7.57 (m, 1H), 7.46 (t, *J* = 7.80 Hz, 2H), 7.43-7.40 (m, 2H), 7.39-7.32 (m, 2H), 7.21 (d, *J* = 8.03 Hz, 2H), 7.16 (ddd, *J* = 8.57, 6.62, 0.79 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 186.01, 148.49, 139.02, 138.15, 137.94, 133.49, 132.21, 129.94, 129.65, 128.62, 126.86, 125.30, 124.86, 124.02, 120.55, 118.53, 77.28, 77.03, 76.77, 21.16. HRMS (ESI) calcd. for $C_{21}H_{16}N_2O$ $[M+H]^+$ 313.1296, found 313.1298.

(2-(4-Chlorophenyl)-2*H*-indazol-3-yl)-(phenyl)-methanone (4b). Yellow solid in a yield of 64% (55 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82-7.77 (m, 3H), 7.55 (t, *J* = 7.46 Hz, 1H), 7.42-7.37 (m, 5H), 7.34-7.30 (m, 2H), 7.23 (d, *J* = 8.61 Hz, 1H), 7.09 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 185.81, 148.67, 139.02, 137.69, 134.93, 133.86, 133.63, 132.27, 130.18, 129.98, 129.73, 129.30, 128.80, 128.47, 127.31, 126.78, 125.32, 124.07, 122.09, 120.59, 118.56, 77.34, 77.09, 76.83. HRMS (ESI) calcd. for $C_{20}H_{13}ClN_2O$ $[M+H]^+$ 334.0687, found 334.0680.

1-(2-(*p*-Tolyl)-2*H*-indazol-3-yl)-butan-1-one (4c). Yellow solid in a yield of 86% (62 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.44 Hz, 1H), 7.86 (td, *J* = 8.65, 0.92 Hz, 1H), 7.42-7.38 (m, 1H), 7.38-7.33 (m, 3H), 7.31 (d, *J* = 8.26 Hz, 2H), 2.82 (t, *J* = 7.23 Hz, 2H), 2.46 (s, 3H), 1.76-1.68 (m, 2H), 0.93 (t, *J* = 7.41 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.97, 148.42, 139.50, 139.05, 133.05, 129.61, 126.78, 125.91, 125.74, 122.97, 120.83, 118.92, 77.29, 77.04, 76.78, 44.35, 21.29, 17.46, 13.75. HRMS (ESI) calcd. for $C_{18}H1_8N_2O$ $[M+H]^+$ 279.1453, found 279.1519.

1-(2-(4-Chlorophenyl)-2*H*-indazol-3-yl)-butan-1-one (4d). Yellow solid in a yield of 85% (66 mg). ^{1}H NMR (500 MHz, $CDCl_3$): 7.99 (dd, *J* = 8.31, 1.21 Hz, 1H), 7.87 (td, *J* = 5.14, 1.06, 1.06 Hz, 1H), 7.52-7.47 (m, 2H), 7.46-7.38 (m, 4H), 2.98 (t, *J* = 7.23, 7.23 Hz, 2H), 1.81-1.73 (m, 2H), 1.00 (t, *J* = 7.41, 7.41 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.34, 147.57, 139.04, 134.22, 131.57, 128.08, 126.43, 126.00, 125.12, 121.70, 119.58, 118.08, 76.28, 76.03, 75.77, 43.40, 16.25, 12.78, 0.00. HRMS (ESI) calcd. for $C_{17}H_{15}ClN_2O$ $[M+H]^+$ 300.0843, found 300.0798.

1-(2-Phenyl-2*H*-[1,3]dioxolo[4,5-*f*]indazol-3-yl)-butan-1-one (4e). Yellow solid in a yield of 77% (62 mg). ^{1}H NMR (500 MHz, $CDCl_3$): 7.54-7.49 (m, 3H), 7.47-7.43 (m, 2H), 7.28 (s, 1H), 7.07 (s, 1H), 6.05 (s, 2H), 2.65 (t, *J* = 7.27, 7.27 Hz, 2H), 1.72-1.63 (m, 2H), 0.89 (t, *J* = 7.40, 7.40 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 191.13, 149.51, 148.84, 145.99, 141.46, 133.15, 129.14, 129.07, 126.12, 119.98, 101.57, 96.25, 94.90, 77.32, 77.06, 76.81, 44.11, 17.50, 13.74. HRMS (ESI) calcd. for $C_{18}H_{16}N_2O_3$ $[M+H]^+$ 309.1194, found 309.1219.

1-(2-(Pyridin-2-yl)-2*H*-indazol-3-yl)-butan-1-one (4f). Yellow solid in a yield of 42% (29 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (dd, *J* = 4.84, 1.03 Hz, 1H), 7.96 (dt, *J* = 7.77, 7.61, 1.82 Hz, 1H), 7.87 (d, *J* = 8.64 Hz, 2H), 7.83 (d, *J* = 8.76 Hz, 1H), 7.44-7.38 (m, 2H), 7.30 (ddd, *J* = 8.46, 6.65, 0.72 Hz, 1H), 2.92 (dd, *J* = 8.83, 5.76 Hz, 2H), 1.88-1.73 (m, 2H), 0.99 (t, *J* = 7.42, 7.42 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.35, 152.83, 148.95, 148.36, 138.80, 133.68, 127.57, 125.41, 123.94, 122.31, 120.53, 118.79, 118.67, 77.32, 77.06, 76.81, 45.05, 17.67, 13.79. HRMS (ESI) calcd. for $C_{16}H_{15}N_3O$ $[M+H]^+$ 266.1249, found 266.1318.

1-(2-(Pyridin-2-yl)-2*H*-indazol-3-yl)-propan-1-one (4g). Yellow solid in a yield of 46% (30 mg).^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (td, *J* = 5.32, 2.66, 2.66 Hz, 1H), 7.99-7.92 (m, 1H), 7.90-7.85 (m, 2H), 7.83 (d, *J* = 8.76 Hz, 1H), 7.44-7.37 (m, 2H), 7.33-7.27 (m, 1H), 2.96 (q, *J* = 7.24, 7.24, 7.23 Hz, 2H), 1.25 (t, *J* = 7.24, 7.24 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.79, 152.87, 148.96, 148.40, 138.81, 133.46, 127.57, 125.44, 123.97, 122.31, 120.56, 118.80, 118.70, 77.32, 77.07, 76.81, 36.46, 8.18. HRMS (ESI) calcd. for $C_{15}H_{13}N_3O$ $[M+H]^+$ 252.1092, found 252.1160.

1-(5-Fluoro-2-(pyridin-2-yl)-2*H*-indazol-3-yl)-butan-1-one (4h). Yellow solid in a yield of 41% (30 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (ddd, *J* = 4.82, 1.73, 0.70 Hz, 1H), 7.99-7.94 (m, 1H), 7.85-7.80 (m, 2H), 7.48 (dd, *J* = 9.16, 1.93 Hz, 1H), 7.44 (ddd, *J* = 7.46, 4.87, 0.99 Hz, 1H), 7.21 (dt, *J* = 9.18, 2.38 Hz, 1H), 2.84 (t, *J* = 7.28 Hz, 2H), 1.82-1.74 (m, 2H), 0.98 (t, *J* = 7.43 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.66, 161.56, 159.61, 152.73, 148.44, 146.31, 138.86, 134.05, 133.98, 124.14, 122.31, 122.22, 121.16, 121.09, 119.52, 119.29, 118.74, 103.66, 103.45, 77.29, 77.04, 76.78, 44.80, 17.61, 13.75. HRMS (ESI) calcd. for $C_{16}H_{14}FN_3O$ $[M+H]^+$ 284.1154, found 284.1204.

(4-Chlorophenyl)-(2-(pyridin-2-yl)-2*H*-indazol-3-yl)-methanone (4i). Yellow solid in a yield of 38% (33 mg). 1H NMR (500 MHz, DMSO- d_6) δ 8.22-8.20 (m, 1H), 8.16-8.07 (m, 2H), 7.91 (d, *J* = 8.84 Hz, 1H), 7.76-7.69 (m, 2H), 7.56-7.50 (m, 3H), 7.48 (m, 1H), 7.41 (ddd, *J* = 7.17, 4.85, 1.24 Hz, 1H), 7.28 (ddd, *J* = 8.52, 6.60, 0.67 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 185.77, 166.96, 151.36, 148.91, 148.39, 140.31, 138.74, 138.26, 136.60, 131.83, 131.61, 131.08, 130.13, 129.47, 129.20, 128.60, 125.60, 124.60, 123.53, 120.51, 118.76, 117.69, 40.43, 40.36, 40.27, 40.19, 40.10, 39.93, 39.77, 39.60, 39.43. HRMS (ESI) calcd. for $C_{19}H_{12}ClN_3O$ $[M+H]^+$ 334.0749, found 334.0810.

(2-(Pyridin-2-yl)-2*H*-indazol-3-yl)-(thiophen-3-yl)-methanone (4j). Yellow solid in a yield of 52% (41 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 4.84, 1.01 Hz, 1H), 7.97 (d, *J* = 8.13 Hz, 1H), 7.86-7.79 (m, 2H), 7.76 (d, *J* = 8.83 Hz, 1H), 7.53-7.48 (m, 2H), 7.31 (ddd, *J* = 8.80, 6.60, 0.99 Hz, 1H), 7.26 (dd, *J* = 5.10, 2.93 Hz, 1H), 7.20-7.17 (m, 1H), 7.11 (ddd, *J* = 8.56, 6.60, 0.73 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 180.37, 167.32, 151.92, 149.03, 148.16, 142.57, 138.77, 134.60, 134.38, 133.02, 128.15. HRMS (ESI) calcd. for $C_{17}H_{11}N_3OS$ $[M+H]^+$ 306.0605, found 306.0758.

Phenyl-(2-(pyridin-2-yl)-2H-indazol-3-yl)-methanone (4k). Yellow solid in a yield of 76% (59 mg). 1H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 4.82, 1.04 Hz, 1H), 8.05 (d, *J* = 8.15 Hz, 1H), 7.88-7.83 (m, 4H), 7.53 (t, *J* = 7.42, 7.42 Hz, 1H), 7.48 (d, *J* = 8.60 Hz, 1H), 7.43-7.35 (m, 3H), 7.20 (dd, *J* = 7.36, 4.88 Hz, 1H), 7.15 (q, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 187.13, 171.60, 151.81, 149.10, 148.02, 138.72, 137.94, 133.73, 133.25, 132.52, 130.21, 129.52, 129.41, 128.58, 128.49, 127.86, 124.72, 123.69, 123.36, 120.60, 118.42, 117.37, 77.31, 77.05, 76.80. HRMS (ESI) calcd. for $C_{19}H_{13}N_3O$ $[M+H]^+$ 300.1092, found 300.1124.

(5-Fluoro-2-(pyridin-2-yl)-2H-indazol-3-yl)-(phenyl)-methanone (4l). Yellow solid in a yield of 45% (37 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 4.84, 1.01 Hz, 1H), 7.93 (d, *J* = 8.13 Hz, 1H), 7.80 (dt, *J* = 8.03, 7.81, 1.81 Hz, 1H), 7.78-7.74 (m, 3H), 7.51-7.46 (m, 1H), 7.38-7.33 (m, 2H), 7.15 (ddd, *J* = 7.46, 4.88, 0.91 Hz, 1H), 7.12 (dt, *J* = 9.21, 9.18, 2.41 Hz, 1H), 6.99 (dd, *J* = 8.96, 1.90 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 186.62,

160.97, 159.02, 151.70, 148.08, 146.48, 138.76, 137.74, 133.67, 133.36, 130.19, 129.43, 128.66, 128.47, 123.53, 120.81, 120.73, 119.91, 119.67, 117.38, 103.38, 103.18, 77.31, 77.05, 76.80. HRMS (ESI) calcd. for $C_{19}H_{12}FN_3O$ $[M+H]^+$ 318.0998, found 318.1073.

3-(*tert*-Butyl)-2-(pyridin-2-yl)-2*H*-indazole (4m). Yellow solid in a yield of 29% (19 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (ddd, *J* = 4.87, 1.86, 0.76 Hz, 1H), 7.95 (td, *J* = 8.82, 0.94, Hz, 2H), 7.90 (td, *J* = 7.75, 1.91 Hz, 1H), 7.68 (td, *J* = 8.75, 0.94 Hz, 1H), 7.54 (td, *J* = 7.91, 0.89, Hz, 1H), 7.28 (ddd, *J* = 8.73, 6.55, 0.98 Hz, 1H), 7.04 (ddd, *J* = 8.79, 6.55, 0.97 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.43, 148.26, 138.21, 126.32, 124.50, 122.72, 121.04, 118.04, 116.56, 77.32, 77.07, 76.81, 34.86, 31.57, 31.25.HRMS (ESI) calcd. for $C_{16}H_{17}N_3$ $[M+H]^+$ 252.1456, found 252.1552.

3-(*tert*-Butyl)-5-fluoro-2-(pyridin-2-yl)-2*H*-indazole (4n). Yellow solid in a yield of 28% (20 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ8.62-8.60 (m, 1H), 7.92 (dt, *J* = 7.73, 7.70, 1.87 Hz, 1H), 7.64 (td, *J* = 14.95, 7.42, 7.42 Hz, 1H), 7.57-7.50 (m, 2H), 7.50-7.45 (m, 1H), 7.10 (dt, *J* = 9.08, 9.06, 2.36 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.45, 156.55, 155.25, 148.36, 146.30, 138.34, 124.62, 122.57, 120.04, 119.96, 118.78, 118.14, 117.91, 105.25, 105.05, 77.29, 77.03, 76.78, 31.40. HRMS (ESI) calcd. for $C_{16}H_{16}FN_3$ $[M+H]^+$ 270.1362, found 270.1431.

Conclusions

In summary, it was achieved an economic and efficient method for the direct C3-acylation of 2*H*-indazoles to react with aldehydes at 80°C using catalyst $NiCl_2$, oxidant TBHP, additive PivOH in the argon environment. The developed approach may increase the molecular diversity of 2*H*-indazoles, promoting the development of biological and pharmaceutical applications of 2*H*-indazole derivatives to some extent.

Conflicts of interest

There are no conflicts to declare.

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