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A mild and regioselective Ullmann reaction of indazoles with aryliodides in water

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ABSTRACT

A mild and regioselective Ullmann reaction of indazoles with aryliodides has been developed as a general method for the synthesis of 1-aryl-1*H*-indazoles. Water was used as the solvent wherein Tween 20 (2% w/w) was added to form aqueous micelles to improve solubility of starting materials and accelerate reaction rate. This aqueous protocol allows the Ullmann reaction to proceed at a mild temperature (60 °C) within a short reaction time (2 h), which typically requires high temperatures (≥100 °C) and prolonged duration (≥24 h). The protocol demonstrated broad substrate scopes with good isolated yields and high regioselectivity (*N*-1 arylation over *N*-2 arylation) for 25 examples examined.

1. Introduction

1-Aryl-1*H*-indazole and its analogs are important building blocks widely applied in a variety of biologically active compounds[1] including Factor Xa inhibitors,[2] GR agonists,[3] KHK inhibitors,[4] and Nav1.7 blockers.[5] Given its prevalence in pharmaceutical industry, a number of strategies have been developed for the construction of the 1-aryl-1*H*-indazole scaffold during the past years including the palladium-catalyzed intramolecular amination of aryliodides,[6] the copper promoted Chan-Lam reaction,[7] the Buchwald-Hartwig coupling,[8] and the Ullmann reaction.[9] Among them, copper-catalyzed Ullmann reaction of indazoles with aryliodides represents one of the most straightforward and atom-economic methods. Buchwald's group[10] described a regioselective synthesis of 1-aryl-1*H*-indazole via copper-catalyzed Ullmann reaction in toluene, wherein elevated temperature (110 °C) and prolonged reaction time (24 h) were required for good conversions. A ligand-free Cu_2O-catalyzed strategy for Ullmann coupling of indazoles in water was reported by Lim and co-workers.[11] Again, they observed the same phenomenon that the reactions proceeded at high temperature (130 °C) and completed in prolonged duration (24 h). Teo and co-workers developed a milder Ullmann coupling condition at 60 °C in water, but the addition of a second metal catalyst (MnF_2) and prolonged reaction time (24 h) were required in order to achieve good conversions.[12] Yao and Zhang's groups reported *N*-(1-oxy-2-picolyl)oxalamic acids as the novel ligand for the Cu-catalyzed *N*-arylation of indazoles and pyrazoles. Harsh reaction conditions were observed (>90 °C, 48 h) with limited examples evaluated.[13] A copper-catalyzed protocol for the cross-coupling of indazole with *p*-tolyl boronic acid was reported to proceed at room temperature, however with low regioselectivity (*N*-1 arylation over *N*-2 arylation).[7] Up to date, the reported protocols are often associated with obvious disadvantages such as high reaction temperature, long reaction time, narrow functional group tolerance, and/or low regioselectivity thus their synthetic utilities are limited. Herein, we report a mild, efficient, and regioselective Ullmann reaction of indazoles with aryliodides for the synthesis of 1-aryl-1*H*-indazoles with a broad substrate scope. The protocol has been developed in the most environmentally friendly and economical solvent, water, which provides additional attractiveness of the methodology.

Replacing organic solvents especially hazardous ones with water has intrigued great attention from both academia and industry to address the significant health and environmental concerns.[14] In order to improve the solubility of organic reactants in water,

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surfactants are employed as additives to water to form aqueous micelles which dissolve organics.[15] Hydrophobic tails of surfactants form micellar "nano-reactors" in water, which favor the compartmentalization of organic reactants in these "nano-reactors" thus increasing the local reaction concentration.[16] Hence, the aqueous micellar solvent enables faster reaction rates and milder reaction temperatures comparing with organic solvents.[17] Our group has successfully developed several novel protocols in this aqueous micellar system with mild reaction conditions, wide scopes of substrates and high yields, including selective *N*-alkylation of 2-pyridones,[18] carboxylate-directed C-H arylation[19] and C2-selective arylation of indoles.[20] In our protocols, Tweens[21] were used as the surfactants due to their commercial availability and relatively nontoxic profile.

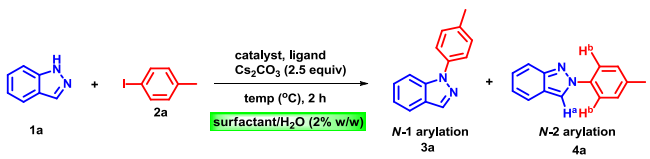
2. Results and discussion

We initiated our exploration of Ullmann reaction using indazole (**1a**) and iodobenzene (**2a**) as model substrates, and Tween 20 as the surfactant to construct the 1-aryl-1*H*-indazole scaffold. (Table 1). It was encourging to find that 20% conversion to the desired product was observed within 2 h using CuBr (10 mol %) as the catalyst, Cs_2CO_3 as the base, and *trans*-*N*1,*N*2-dimethylcyclohexane-1,2-diamine as the ligand in Tween 20/water micellar solvent (2% w/w) at room temperature (entry 1). Based on HPLC-MS analysis, the ratio of *N*-1 arylation product **3a** and *N*-2 arylation product **4a** was observed to be 6:1 (entry 1), consistent with the kinetically preferred copper–indazole (*N*-1) intermediate during the reaction.[10] The structure assignment of **3a** was indirectly confirmed from 2D NMR spectroscopy based on the NOESY cross-peaks between H^a and H^b of **4a** (Supporting Information). The structure assignment was further confirmed by comparison of the spectroscopic data of **3a** with those reported in literature.[22] With the encouraging preliminary result, we then investigated the effect of different copper(I) catalysts on the reaction including CuI (entry 2), CuTC (entry 3), CuCN (entry 4), and Cu_2O (entry 5) and the rest copper catalysts resulted in much lower conversion even with prolonged reaction time. In addition to the catalyst, the surfactants were also observed to significantly impact on the reactivity of the Ullmann coupling reaction. TPGS-750-M (entry 6), TritonX-100 (entry 7), Brij30 (entry 8) and PEG-600 (entry 9) resulted in much decreased conversion (≤27%) to the Ullmann coupling product 3a comparing to that of Tween 20 (42%). Further, different sizes of Tweens were evaluated and slightly lower reactivity relative to Tween 20 was observed when Tween 40 (entry 10), Tween 60 (entry 11), and Tween 80 (entry 12) were used as surfactants. Among the surfactants evaluated, Tween 20 proved to be superior considering both conversion and regioselectivity, notwithstanding a higher regioselectivity observed for PEG-600 (lower conversion however). On the other hand, the reaction proceeded with low conversion without the addition of surfactant (entry 13), which was likely due to low solubility of starting materials as well as the copper catalyst in water. Increasing the catalyst loading from 10 mol% to 20 mol% resulted in accelerated reaction rate, providing 60% conversion (entry 14). When the temperature was increased to 60 °C, a full conversion was observed (99%, entry 15) at the same time the regioselectivity was maintained (*N*-1/*N*-2 arylation ratio = 5:1). The optimal condition for the Ullmann reaction was thus concluded using Tween 20/water (2% w/w) as the solvent, CuI (20 mol%) as the catalyst, and at elevated temperature (60 °C).

The optimal reaction condition was then applied to the Ullmann reaction of indazole (**1a**) with a broad scope of aryliodides (**2**). As showed in Table 2, iodobenzenes with a variety of different substitutions were well tolerated for the reaction. Overall, high conversions were observed and good isolated yields of desired 1-aryl-1*H*-indazole products (**3**) were obtained with a couple of exceptions (**3h** and **3i**). In addition, the regioselectivity (*N*-1/*N*-2 arylation ratio) was observed high (5:1 to 10:1) as determined by integration of the characteristic protons for products **3** and **4** in ^{1}H NMR spectra of the crude reaction mixtures. *Para*-substituted iodobenzenes bearing both electron-donating substitutions such as $-CH_3$, $-OCH_3$ and electron-withdrawing substitutions including $-Cl$, $-CN$, $-COOMe$, or $-CF_3$ resulted in good to excellent conversions (entries 1–6, 61%–98%) and provided the desired 1-aryl-1*H*-indazole products (**3a**–**3f**) with good isolated yields (50%–83%). The methyl ester substitution was tolerated with the reaction condition even though a relatively lower yield was obtained (entry 5), which might due to partial hydrolysis of the methyl ester under the basic condition in water. Iodobenzene with *meta*-substitution (1-iodo-3-trifluoromethylbenzene, entry 7) demonstrated similar reactivity to provide the Ullmann product (**3g**) in excellent conversion (100%), high *N*-2/*N*-1 arylation ratio (10:1), and good isolated yield (91%). On the other hand, when the trifluoromethyl substitution was on the *ortho*-position (**2h**) no coupling product was observed even after prolonged reaction time (entry 8), indicating the reactivity was sensitive to steric effect. Low yield of the Ullmann coupling product **3i** (38%) was obtained when 4-iodo-1,1'-biphenyl was used as the starting material (entry 9), which might due to its low solubility. Furthermore, heteroaromatic halides were also examined including 2-iodopyrazine (**2j**), 2-bromothiazole (**2k**), and 4-iodo-1-methyl-1*H*-pyrazole (**2l**), and all of them provided good conversions and isolated yields. It is noteworthy that the five-membered heteroaromatic halides (**2k** and **2l**) resulted in very high regioselectivity, with the *N*-1/*N*-2 arylation ratios greater than 99:1 (entries 11 and 12) based on HPLC-MS analysis of the crude reaction mixtures.

The substrate scope of indazoles was also investigated. As

Table 1
Optimization of reaction conditions for Ullmann reaction of indazole.[a]



Entry	Catalyst	Surfactant	Temp (°C)	Conversion (%)[b]	3a/4a ratio[b]
1	CuBr	Tween 20	rt	20	6:1
2	CuI	Tween 20	rt	42	6:1
3	CuTC	Tween 20	rt	25	6:1
4[c]	CuCN	Tween 20	rt	0	ND[d]
5[c]	Cu_2O	Tween 20	rt	0	ND[d]
6	CuI	TPGS-750-M	rt	15	6:1
7	CuI	TritonX-100	rt	6	5:1
8	CuI	Brij30	rt	9	6:1
9	CuI	PEG-600	rt	27	8:1
10	CuI	Tween 40	rt	22	6:1
11	CuI	Tween 60	rt	35	6:1
12	CuI	Tween 80	rt	15	6:1
13	CuI	/	rt	14	6:1
14[e]	CuI	Tween 20	rt	60	4:1
15[e]	CuI	Tween 20	60	99	5:1

[a] Reaction conditions: indazole **1a** (47 mg, 1.0 eq), iodobenzene **2a** (105 mg, 1.2 eq), Cs_2CO_3 (326 mg, 2.5 eq), catalyst (10 mol%), *trans*-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (40 mol%), surfactant/H_2O (2% w/w, 2 mL), 2 h.
[b] Conversion and *N*-1/*N*-2 arylation ratio were determined by HPLC peak areas at 254 nm for indazole **1a** and the regioisomeric products (**3a** and **4a**) in the crude reaction mixture.
[c] 24 h.
[d] No data.
[e] 20 mol% CuI, 80 mol% *trans*-*N*1,*N*2-dimethylcyclohexane-1,2-diamine.

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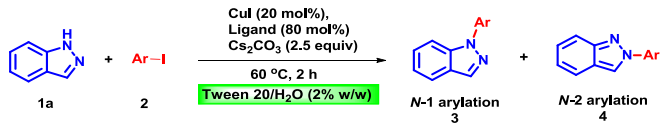
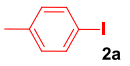
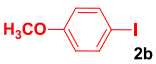
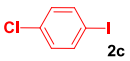
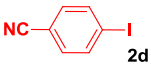
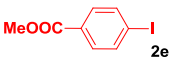
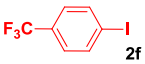
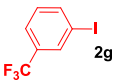
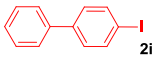
Table 2
Scope of aryl halides for Ullmann reaction in Tween 20/water.[a]



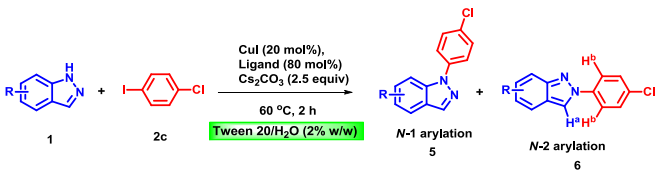
Entry	2	Conversion (%)[b]	3/4 ratio[c]	Isolated yield of 3 (%)
1	 2a	97	6:1	**3a**, 73
2	 2b	95	5:1	**3b**, 79
3	 2c	98	10:1	**3c**, 76
4	 2d	91	10:1	**3d**, 81
5	 2e	61	7:1	**3e**, 50
6	 2f	97	7:1	**3f**, 83
7	 2g	100	10:1	**3g**, 91
8	 2h	0	ND[d]	**3h**, ND[d]
9	 2i	70	5:1	**3i**, 38
10	 2j	89	8:1	**3j**, 78
11	 2k	60	>99:1	**3k**, 58
12	 2l	71	>99:1	**3l**, 67

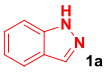
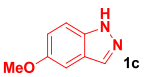
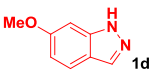
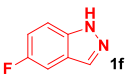
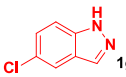
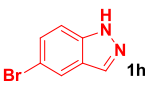
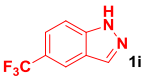
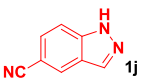
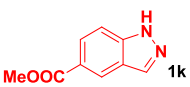
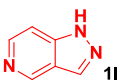
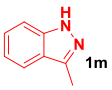
[a] Reaction conditions: indazole **1a** (100 mg, 1.0 eq), arylhalides **2** (1.2 eq), Cs_2CO_3 (2.5 eq), catalyst (20 mol%), *trans*-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (80 mol %), surfactant/H_2O (2% w/w, 2 mL), 2 h.
[b] Conversion was determined by HPLC peak areas at 254 nm for indazole **1a** and both regioisomeric products (**3** and **4**) in the reaction mixture.
[c] *N*-1/*N*-2 arylation ratio was determined by integration of the characteristic protons for products **3** and **4** in ^{1}H NMR spectra of the crude reaction mixture.
[d] No data.

showed in Table 3, indazoles bearing the electron-donating substitution (methoxy) at different positions (4-, 5-, 6-, and 7-position) underwent Ullmann reaction with 1-chloro-4-iodobenzene smoothly, providing corresponding 1-aryl-1*H*-indazole products in moderate to good yields (entries 2–5). Among them, the 7-methoxy-1*H*-indazole (**1e**) provided the lowest regioselectivity (*N*-1/*N*-2 arylation ratio = 3:1) which might be the result of the steric effect of the methoxy group.

We then focused the substrate explorations on 5-substituted indazoles because of their commercial availability. The reaction demonstrated good tolerability for different substitutions including both electron-withdrawing (entries 6–11) and electron-donating groups (entry 3). Excellent regioselectivity (>99:1 and 30:1) was

Table 3
Scope of indazoles for Ullmann reaction in Tween 20/water.[a]



Entry	2	Conversion (%)[b]	5/6 ratio[c]	Isolated yield of 5 (%)
1	 1a	98	10:1	**3c**, 76
2	 1b	87	7:1	**5a**, 75
3	 1c	60	4:1	**5b**, 46
4	 1d	89	8:1	**5c**,74
5	 1e	72	3:1	**5d**, 52
6	 1f	95	6:1	**5e**, 80
7	 1g	100	10:1	**5f**, 86
8	 1h	94	7:1	**5g**,79
9	 1i	80	11:1	**5h**, 71
10	 1j	95	>99:1	**5i**, 86
11	 1k	100	30:1	**5j**, 91
12	 1l	81	>99:1	**5k**, 63
13	 1m	70	>99:1	**5l**, 70

[a] Reaction conditions: indazole **1** (100 mg, 1.0 eq), 1-chloro-4-iodobenzene 2 (1.2 eq), Cs_2CO_3 (2.5 eq), catalyst (20 mol%), *trans*-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (80 mol%), surfactant/H_2O (2% w/w, 2 mL), 2 h.
[b] Conversion was determined by HPLC peak areas at 254 nm for indazoles **1** and both regioisomeric products (**5** and **6**) in the reaction mixture.
[c] *N*-1/*N*-2 arylation ratio was determined by comparing integrations of characteristic protons for product **5** and **6** in ^{1}H NMR spectrum of the crude reaction mixture.

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observed with the cyano and ester substitutions (**1j** and **1k**), likely due to its strong electron-withdrawing property rendering the resulting copper–indazole (*N*-1) intermediate the most dominant than all the other substituents. Similarly, aza-indazole (**1l**) also provided excellent regioselectivity (*N*-1/*N*-2 arylation ratio > 99:1) in good isolated yield (91%, entry 12). Further, introducing a methyl group *ortho* to *N*-2 of indazole (entry 13) afforded a much improved regioselectivity (>99:1) comparing with the un-substituted indazole (10:1, entry 1). Again, the regiochemistry was confirmed from 2D NMR spectroscopy (e.g. observed NOESY cross-peaks between H^a and H^b of **6d**, Supporting Information).

The protocol was further extended to other bicyclic heterocycles (Table 4) in addition to indazoles. To our delight, the reaction worked smoothly on both indole (**7**) and indolin-2-one (**9**), and the desired Ullmann coupling products **8** and **10** were obtained in moderate to good yields (37% and 81%, respectively). The ^{1}H NMR spectrum of **10** was observed identical to that reported in literature,[23] confirming the *N*-arylation regioselectivity over *O*-arylation. The result suggested this aqueous protocol could be generalized as a mild method for the Ullmann reaction of heterocycles.

3. Conclusion

In summary, we have developed a mild, efficient, and regioselective method for the preparation of 1-aryl-1*H*-indazole through copper-catalyzed Ullmann reaction between indazoles and aryliodides in water with 2% (w/w) Tween 20. The aqueous micelles formed enable improved solubility of starting materials and increased local reaction concentration thus accelerated reaction rate. This aqueous protocol allows a mild reaction temperature (60 °C) and a short reaction time (2 h) for the Ullmann reaction, which otherwise requires high temperatures (≥100 °C) and prolonged duration (≥24 h). The protocol also demonstrated broad substrate scopes with good isolated yields and high regioselectivity (*N*-1 over *N*-2 arylation) for the examples examined. In addition, the protocol was further generalized to bicyclic heterocycles other than indazole, such as indole and indolin-2-one, for Ullmann reaction. Further application of this protocol to other heterocyclic substrates is ongoing.

4. Experimental section

4.1. General methods

All reactions were conducted under atmosphere without special drying. All reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR, ^{13}C NMR and 2D NOESY spectra were recorded on a Bruker 400 or 600 NMR spectrometer using $CDCl_3$ (deuterochloroform) as the solvents and TMS (tetramethylsilane) as the internal standard. Chemical shifts (δ)are given in parts per million (ppm) downfield from the TMS signal. The following abbreviations are used to indicate the multiplicity in NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. *J* indicates the NMR coupling constant measured in Hertz. High resolution mass (HRMS) was operated in a positive mode of electrospray ionization (ESI) at an orthogonal acceleration time-of-flight (oa-TOF) SYNAPT G2 HDMSTM (Waters, Manchester, UK). LCMS (Agilent 1200SL-6110) analysis was conducted for all compounds under the acidic condition: acidic condition refers to water containing 0.05% TFA/acetonitrile as the mobile phase on Agilent SB-C18 column (1.8 μm, 4.6 × 30 mm), with MS and photodiode array detector (PDA). The following conditions were used: a gradient from 5 to 95% in 5 min (or 6 min) and held at 95% for 1 min; UV detection at 214 and 254 nm; a flow rate of 1.5 ml/min; full scan; mass range from 100 to 1000 amu. Column chromatography was performed on ISCO or Biotage using a prepacked silica gel column, a detector with UV wavelength at 254 nm and 280 nm.

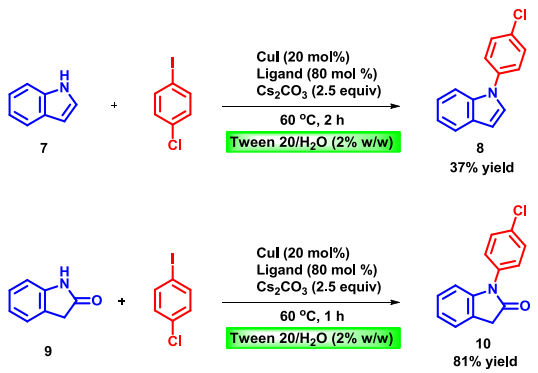
4.2. General procedures for the syntheses of compounds 3, 5, 8 and 10

To a mixture of indazoles, indoles, or indolin-2-ones (1 equiv), aryl halides (1.2 equiv), cesium carbonate (2.5 equiv), copper (I) iodide (0.2 equiv) in Tween 20/water (2%, w/w, 0.2 M) was added *trans*-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (0.8 equiv). The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was extracted with ethyl acetate (20 mL × 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel and eluted with PE/EA to afford the desired product **3, 5, 8** and **10**.

4.2.1. 1-(P-tolyl)-1H-indazole (*3a*)

129 mg (73% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.23 (d, *J* = 0.8 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.44 (ddd, *J* = 0.98, 7.2, 8.4 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.21–7.28 (m, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 138.8, 137.8, 136.6, 135.1, 130.0, 127.0, 125.2, 122.8, 121.3, 110.4, 21.1. LC-MS: 209.1 $[M+H]^+$, t_R = 3.85 min. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}N_2$ $[M+H]^+$

Table 4
Ullmann reaction of indole and indolin-2-one in Tween 20/water.



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209.1079, found $[M+H]^+$ 209.1081.

*4.2.2. 2-(P-tolyl)-2H-indazole (**4a**)*

20 mg (11% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.40 (s, 1H), 7.78–7.85 (m, 3H), 7.73 (d, J = 8.4 Hz, 1H), 7.31–7.38 (m, 3H), 7.13 (dd, J = 6.8, 8.0 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 149.7, 138.3, 137.9, 130.1, 126.7, 122.7, 122.3, 120.9, 120.3, 117.9, 21.0. LC-MS: 209.1 $[M+H]^+$, t_R = 3.61 min.

*4.2.3. 1-(4-Methoxyphenyl)-1H-indazole (**3b**)*

150 mg (79% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.20 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.62–7.71 (m, 3H), 7.43 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 9.2 Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 158.4, 139.0, 134.8, 133.4, 126.9, 125.0, 124.5, 121.3, 114.6, 110.2, 55.6. LC-MS: 225.1 $[M+H]^+$, t_R = 3.47 min. HRMS (ESI): m/z calcd for $C_{14}H_{13}N_2O$ $[M+H]^+$ 225.1028, found $[M+H]^+$ 225.1031.

*4.2.4. 1-(4-Chlorophenyl)-1H-indazole (**3c**)*

150 mg (76% yield) as a white solid. . ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.23 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.68–7.77 (m, 3H), 7.51–7.57 (m, 2H), 7.44–7.51 (m, 1H), 7.26–7.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 138.8, 138.7, 135.8, 132.0, 129.6, 127.4, 125.5, 123.8, 121.8, 121.5, 110.2. LC-MS: 229 $[M+H]^+$, t_R = 3.85 min. HRMS (ESI): m/z calcd for $C_{13}H_{10}N_2Cl$ $[M+H]^+$ 229.0533, found $[M+H]^+$ 229.0535.

*4.2.5. 4-(1H-indazol-1-yl)benzonitrile (**3d**)*

160 mg (81% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.28 (s, 1H), 7.93–8.00 (m, 2H), 7.79–7.90 (m, 4H), 7.54 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 143.8, 138.5, 137.3, 133.6, 128.1, 126.1, 122.5, 121.9, 118.5, 110.4, 109.1. LC-MS: 219.9 $[M+H]^+$, t_R = 3.44 min. HRMS (ESI): m/z calcd for $C_{14}H_{10}N_3$ $[M+H]^+$ 220.0875, found $[M+H]^+$ 220.0871.

*4.2.6. Methyl 4-(1H-indazol-1-yl)benzoate (**3e**)*

110 mg (50% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.19–8.30 (m, 1H), 7.78–7.96 (m, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.29–7.33 (m, 1H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 166.5, 144.0, 138.6, 136.6, 131.1, 127.7, 125.9, 122.1, 121.6, 121.5, 110.6, 51.5. LC-MS: 252.9 $[M+H]^+$, t_R = 3.67 min. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$ 253.0977, found $[M+H]^+$ 253.0980.

*4.2.7. 1-(4-(Trifluoromethyl)phenyl)-1H-indazole (**3f**)*

193 mg (83% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.27 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.78–7.88 (m, 4H), 7.51 (t, J = 8.0 Hz, 1H), 7.21–7.36 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 143.1, 138.6, 136.6, 127.8, 125.9, 122.1, 121.6, 110.3. LC-MS: 263 $[M+H]^+$, t_R = 3.98 min. HRMS (ESI): m/z calcd for $C_{14}H_{10}N_2F_3$ $[M+H]^+$ 263.0796, found $[M+H]^+$ 263.0799.

*4.2.8. 1-(3-(Trifluoromethyl)phenyl)-1H-indazole (**3g**)*

205 mg (91% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.27 (s, 1H), 8.07 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.66–7.74 (m, 1H), 7.60–7.66 (m, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.29–7.34 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 140.8, 138.6, 136.3, 130.1, 127.7, 125.7, 125.3, 122.0, 121.6, 110.1. LC-MS: 263 $[M+H]^+$, t_R = 4.10 min. HRMS (ESI): m/z calcd for $C_{14}H_{10}N_2F_3$ $[M+H]^+$ 263.0796, found $[M+H]^+$ 263.0802.

*4.2.9. 1-([1,1′-Biphenyl]-4-yl)-1H-indazole (**3i**)*

92 mg (38% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.23 (s, 1H), 7.73–7.86 (m, 7H), 7.66 (d, J = 7.6 Hz, 2H), 7.43–7.53 (m, 3H), 7.35–7.42 (m, 1H), 7.24 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture): δ ppm 140.3, 139.5, 138.8, 135.5, 128.9, 128.1, 127.5, 127.2, 127.1, 125.4, 122.9, 121.6, 121.4, 110.5. LC-MS: 271 $[M+H]^+$, t_R = 4.25 min. HRMS (ESI): m/z calcd for $C_{19}H_{15}N_2$ $[M+H]^+$ 271.1235, found $[M+H]^+$ 271.1236.

*4.2.10. 1-(Pyrazin-2-yl)-1H-indazole (**3j**)*

130 mg (78% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.43 (s, 1H), 8.74 (d, J = 8.8 Hz, 1H), 8.43 (d, J = 9.2 Hz, 2H), 8.25 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 150.3, 141.3, 139.8, 139.0, 138.1, 136.5, 128.4, 126.1, 123.2, 121.0, 115.0. LC-MS: 197 $[M+H]^+$, t_R = 3.15 min. HRMS (ESI): m/z calcd for $C_{11}H_9N_4$ $[M+H]^+$ 197.0827, found $[M+H]^+$ 197.0827.

*4.2.11. 2-(1H-indazol-1-yl)thiazole (**3k**)*

99 mg (58% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.65 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 3.6 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 162.7, 140.3, 138.3, 138.0, 128.9, 125.8, 123.4, 121.1, 114.1, 113.9. LC-MS: 202 $[M+H]^+$, t_R = 3.41 min. HRMS (ESI): m/z calcd for $C_{10}H_8N_3S$ $[M+H]^+$ 202.0439, found $[M+H]^+$ 202.0446.

*4.2.12. 1-(1-Methyl-1H-pyrazol-4-yl)-1H-indazole (**3l**)*

115 mg (67% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.16 (s, 1H), 7.89 (s, 1H), 7.77–7.83 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 4.04 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 139.4, 134.9, 132.7, 127.2, 124.5, 124.4, 123.7, 121.4, 121.3, 109.8, 39.6. LC-MS: 198.9 $[M+H]^+$, t_R = 2.60 min. HRMS (ESI): m/z calcd for $C_{11}H_{11}N_4$ $[M+H]^+$ 199.0984, found $[M+H]^+$ 199.0984.

*4.2.13. 1-(4-Chlorophenyl)-4-methoxy-1H-indazole (**5a**)*

130 mg (75% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.29 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.34–7.42 (m, 1H), 7.31 (m, 1H), 6.59 (d, J = 7.6 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 154.0, 140.4, 138.9, 133.6, 132.0, 129.5, 128.8, 123.7, 117.3, 103.0, 100.7, 55.5. LC-MS: 259 $[M+H]^+$, t_R = 3.94 min. HRMS (ESI): m/z calcd for $C_{14}H_{12}N_2OCl$ $[M+H]^+$ 259.0638, found $[M+H]^+$ 259.0644.

*4.2.14. 1-(4-Chlorophenyl)-5-methoxy-1H-indazole (**5b**)*

81 mg (46% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.13 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 9.2 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.09–7.18 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 155.2, 138.9, 135.1, 134.5, 131.9, 129.6, 126.0, 123.4, 121.6, 119.3, 111.3, 100.7, 55.7. LC-MS: 259 $[M+H]^+$, t_R = 3.84 min. HRMS (ESI): m/z calcd for $C_{14}H_{12}N_2OCl$ $[M+H]^+$ 259.0638, found $[M+H]^+$ 259.0641.

*4.2.15. 1-(4-Chlorophenyl)-6-methoxy-1H-indazole (**5c**)*

130 mg (74% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.11 (s, 1H), 7.68 (d, J = 8.4 Hz, 3H), 7.54 (d, J = 8.8 Hz, 2H), 7.06 (s, 1H), 6.92 (dd, J = 2.0, 8.8 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 160.2, 140.2, 138.8, 135.8, 132.0, 129.6, 123.9, 122.1, 121.5, 120.0, 113.4, 91.7, 55.6. LC-MS: 259 $[M+H]^+$, t_R = 3.89 min. HRMS (ESI): m/z calcd for $C_{14}H_{12}N_2OCl$ $[M+H]^+$ 259.0638, found $[M+H]^+$ 259.0638.

*4.2.16. 1-(4-Chlorophenyl)-7-methoxy-1H-indazole (**5d**)*

90 mg (52% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.18 (s, 1H), 7.50–7.57 (m, 2H), 7.37–7.47 (m, 3H), 7.18 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 146.1, 139.8, 135.8, 132.6, 130.3, 128.1, 127.4, 127.1, 122.4, 113.2, 106.8, 55.4. LC-MS: 259 $[M+H]$,

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t_R = 3.79 min. HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_2OCl$ $[M+H]^+$ 259.0638, found $[M+H]^+$ 259.0640.

*4.2.17. 2-(4-Chlorophenyl)-7-methoxy-2H-indazole (**6d**)*

27 mg (16% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.35 (s, 1H), 7.84–7.98 (m, 2H), 7.39–7.53 (m, 2H), 7.20–7.32 (m, 1H), 7.05 (dd, *J* = 7.4, 8.4 Hz, 1H), 6.61 (d, *J* = 7.34 Hz, 1H), 4.07 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, mixture): δ ppm 150.4, 143.5, 138.9, 133.5, 129.5, 124.5, 123.4, 122.1, 120.5, 112.3, 103.4, 55.5. LC-MS: 259 [M+H], t_R = 3.58 min.

*4.2.18. 1-(4-Chlorophenyl)-5-fluoro-1H-indazole (**5e**)*

140 mg (80% yield) as an orange solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.19 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 3H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.45 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.20–7.28 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$,): δ ppm 159.4, 157.0, 138.4, 135.7, 135.4, 132.4, 129.7, 123.7, 117.0, 116.7, 111.3, 105.5.^{19}F NMR (376 MHz, $CDCl_3$): δ ppm 121.60 (s, 1F). LC-MS: 247 $[M+H]^+$, t_R = 4.00 min. HRMS (ESI): *m/z* calcd for $C_{13}H_9N_2ClF$ $[M+H]^+$ 247.0438, found $[M+H]^+$ 247.0444.

*4.2.19. 5-Chloro-1-(4-chlorophenyl)-1H-indazole (**5f**)*

149 mg (91% yield) as an orange solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.17 (s, 1H), 7.80 (br s, 1H), 7.63–7.71 (m, 3H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.42 (dd, *J* = 2.0, 9.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 138.4, 137.2, 135.0, 132.5, 129.7, 128.0, 127.4, 126.3, 123.8, 120.6, 111.3. LC-MS: 263 $[M+H]^+$, t_R = 4.17 min. HRMS (ESI): *m/z* calcd for $C_{13}H_9N_2Cl_2$ $[M+H]^+$ 263.0143, found $[M+H]^+$ 263.0142.

*4.2.20. 5-Bromo-1-(4-chlorophenyl)-1H-indazole (**5g**)*

123 mg (79% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.17 (s, 1H), 7.97 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.60 (s, 1H), 7.49–7.57 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 138.3, 137.4, 134.9, 132.6, 130.5, 129.7, 127.0, 123.9, 123.8, 122.1, 114.8, 111.6. LC-MS: 306.9 $[M+H]^+$, t_R = 4.26 min. HRMS (ESI): *m/z* calcd for $C_{13}H_9N_2ClBr$ $[M+H]^+$ 306.9638, found $[M+H]^+$ 306.9643.

*4.2.21. 1-(4-Chlorophenyl)-5-(trifluoromethyl)-1H-indazole (**5h**)*

113 mg (71% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.33 (s, 1H), 8.16 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 3H), 7.57 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 139.7, 138.1, 136.5, 133.0, 129.8, 124.1, 124.0, 119.6, 110.8.^{19}F NMR (376 MHz, $CDCl_3$): δ ppm −61.08 (s, 1F). LC-MS: 297$[M+H]^+$, t_R = 4.23 min. HRMS (ESI): *m/z* calcd for $C_{14}H_9N_2ClF_3$ $[M+H]^+$ 297.0406, found $[M+H]^+$ 297.0407.

*4.2.22. 1-(4-Chlorophenyl)-1H-indazole-5-carbonitrile (**5i**)*

152 mg (86% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.34 (s, 1H), 8.24 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 3H), 7.50–7.61 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 139.5, 137.7, 136.3, 133.4, 129.9, 129.6, 127.8, 125.0, 124.3, 119.2, 111.4, 105.4. LC-MS: 254 $[M+H]^+$, t_R = 3.63 min. HRMS (ESI): *m/z* calcd for $C_{14}H_9N_3Cl$ $[M+H]^+$ 254.0485, found $[M+H]^+$ 254.0491.

*4.2.23. Methyl 1-(4-chlorophenyl)-1H-indazole-5-carboxylate (**5j**)*

148 mg (91% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.60 (s, 1H), 8.33 (s, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.67–7.79 (m, 3H), 7.56 (d, *J* = 8.8 Hz, 2H), 3.99 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 166.9, 140.5, 138.2, 137.1, 129.7, 128.3, 125.2, 124.8, 124.0, 109.2, 52.2. LC-MS: 287$[M+H]^+$, t_R = 3.87 min. HRMS (ESI): *m/z* calcd for $C_{15}H_{12}N_2O_2Cl$ $[M+H]^+$ 287.0587, found $[M+H]^+$ 287.0591.

*4.2.24. 1-(4-Chlorophenyl)-1H-pyrazolo[4,3-c]pyridine (**5k**)*

122 mg (63% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 9.21 (s, 1H), 8.54 (d, *J* = 6.0 Hz, 1H), 8.38 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 145.9, 145.2, 141.4, 137.8, 135.7, 133.0, 129.9, 123.7, 122.6, 105.0. LC-MS: 230$[M+H]^+$, t_R = 2.08 min. HRMS (ESI): *m/z* calcd for $C_{12}H_9N_3Cl$ $[M+H]^+$ 230.0485, found $[M+H]^+$ 230.0489.

*4.2.25. 1-(4-Chlorophenyl)-3-methyl-1H-indazole (**5l**)*

130 mg (70% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.76 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 3H), 7.42–7.54 (m, 3H), 7.21–7.27 (m, 1H), 2.68 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 144.4, 139.4, 138.9, 131.4, 129.5, 127.4, 125.1, 123.3, 121.1, 120.8, 110.1, 11.9. LC-MS: 243$[M+H]^+$, t_R = 4.07 min. HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_2Cl$ $[M+H]^+$ 243.0689, found $[M+H]^+$ 243.0689.

*4.2.26. 1-(4-Chlorophenyl)-1H-indole (**8**)*

72 mg (37% yield) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.71 (d, *J* = 7.6 Hz, 1H), 7.41–7.58 (m, 5H), 7.32 (d, *J* = 3.2 Hz, 1H), 7.17–7.27 (m, 2H), 6.72 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 138.4, 135.7, 132.0, 129.8, 129.4, 127.7, 125.5, 122.6, 121.3, 120.6, 110.3, 104.1. LC-MS: 228$[M+H]^+$, t_R = 2.08 min. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}NCl$ $[M+H]^+$ 228.058, found $[M+H]^+$ 228.0578.

*4.2.27. 1-(4-Chlorophenyl)indolin-2-one (**10**)*

148 mg (81% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.53 (d, *J* = 8.8 Hz, 2H), 7.31–7.43 (m, 3H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.06–7.16 (m, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.74 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ ppm 174.3, 144.8, 133.7, 133.1, 129.9, 127.9, 124.8, 124.3, 123.1, 109.3, 36.0. LC-MS: 244$[M+H]^+$, t_R = 4.20 min. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}NOCl$ $[M+H]^+$ 244.0529, found $[M+H]^+$ 244.0529.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.11.066.

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