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Iodine-mediated construction of polyfunctionalized arylazopyrazoles from β-ketoesters or 2-arylpyrazol-3-ones and arylhydrazines†

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This paper describes step-economic iodine-mediated construction of functionalized arylazopyrazoles in the presence of catalytic $AgNO_3$ starting from simple β-ketoesters and two equivalents of arylhydrazines. This cascade reaction includes *in situ* α-iodination of β-ketoesters, pyrazol-3-one formation, substitution with a nitrogen nucleophile, and oxidation/aromatization.

Introduction

Pyrazoles (or arylpyrazoles) are heteroaromatic compounds possessing a wide range of biological and pharmacological properties.[1–9] These pyrazole-containing molecules have potent anti-inflammatory,[1] antifungal,[2] antibacterial,[3] antiviral,[4] analgesic,[5] antipyretic,[6] and protein kinase inhibitory activities.[7] Some of them are currently used as commercialized medicines, such as rimonabant (**1**), celecoxib (**2**), and the insecticide, fipronil (**3**) (Fig. 1).[8] Pyrazoles are also used as building blocks for the synthesis of bioactive natural products, agrochemicals, and medicines.[9]

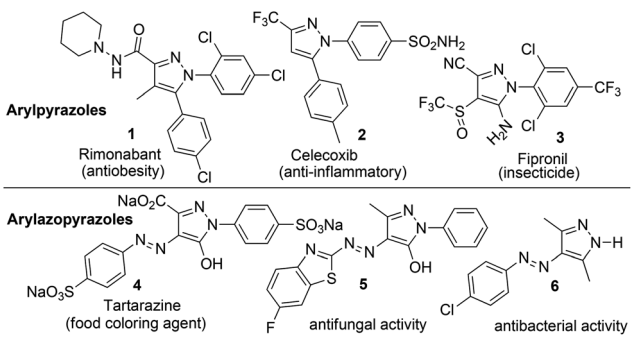

Fig. 1 Selected examples of bioactive molecules bearing the arylpyrazole and arylazopyrazole skeleton.

Azopyrazoles (or arylazopyrazoles) are also distributed as the core structure in many food colorings, dyes and bioactive compounds (Fig. 1).[10] They exhibit biological activities, such as antifungal,[11] antibacterial,[12] and HIV-1 inhibitory properties.[13] Recently, arylazopyrazoles have been widely used as important photoswitches offering quantitative isomerization[14] and light-responsive molecular switches in cyclodextrin-based supramolecular systems.[15] Because of their medicinal and industrial significance, several synthetic methods for azopyrazoles and arylazopyrazoles have been developed over the past decade.[16] Most of the synthetic strategies rely on the coupling of diazotized salts with ketoesters[12–13,16a] and direct derivatization from pyrazoles.[16] Despite these achievements, they suffer from certain drawbacks including the requirement of multiple synthetic steps, raw material availability, harsh reaction conditions, and low yield.

Recently, we have developed a novel method for the synthesis of diverse arylazopyrazoles by a silver-catalyzed cascade reaction of diazo compounds with aryl hydrazines (Scheme 1).[17] Nevertheless, more environmentally benign and simple approaches for the construction of arylazopyrazoles from commercially available starting materials with high diversity are still in strong demand. As a part of an ongoing study on the development of a safer and more reliable synthetic methodology for arylazopyrazoles, we describe an iodine-mediated cascade process for the construction of polyfunctio-

Scheme 1 Our previous strategy for the synthesis of arylazopyrazoles from diazo compounds.

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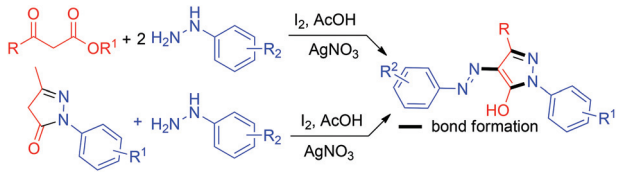


Scheme 2 New synthetic strategy for the construction of multifunctionalized arylazopyrazoles.

nalized arylazopyrazoles using commercially available β-ketoesters or 2-arylpyrazol-3-ones instead of the corresponding diazo compounds (Scheme 2). The current method avoids the use of prefunctionalized and potential explosive α-diazo compounds and features pseudo three-component reactions that can install two different hydrazine moieties in the same molecule.

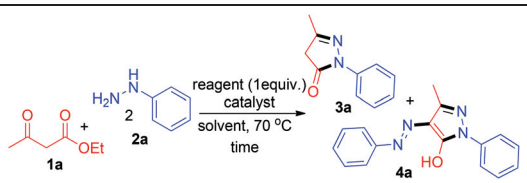
Results and discussion

This study was initiated by examining the reaction of ethyl acetoacetate (**1a**) with two equivalents of phenylhydrazine (**2a**) as model substrates to obtain an arylazopyrazole (Table 1).

A reaction of **1a** with **2a** in acetonitrile at 70 °C for 12 h provided **3a** in 53% yield (entry 1) without the isolation of the expected arylazopyrazole **4a**. With 10 mol% of AgOTf as a catalyst, the yield of **3a** was increased to 65% (entry 2) along with isolation of 5% of the desired product **4a**. The reaction was next attempted using halogenating reagents to transform β-ketoester **1a** into arylazopyrazole. The treatment of **1a** with **2a** in the presence of one equivalent of iodine in acetonitrile at 70 °C for 12 h provided the product **3a** in 90% yield (entry 3) along with 5% of arylazopyrazole. With iodine (1 equiv.) and acetic acid (1 equiv.), the product **4a** was obtained in 45% yield (entry 4). Importantly, the addition of several silver salts (AgOTf, AgOAc, $AgNO_3$, Ag_2O, and Ag_2CO_3) as a catalyst in different solvents provided the desired product **4a** in higher yield (entries 5–14). Among these, when the reaction was carried out in the presence of iodine/acetic acid using 10 mol% $AgNO_3$ in 1,2-dichloroethane, **4a** was produced in the highest yield (85%) (entry 12) without detection of **3a** rather, the complete conversion of **1a** took place in just 6 h under the above conditions. In other nonpolar or polar solvents, the yield of **4a** did not improve. The use of other halogenating reagents, such as *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) in combination with acetic acid and 10 mol% $AgNO_3$ was less effective than iodine/acetic acid (entries 15 and 16). In addition, the role of 2-iodoxybenzoic acid (IBX) as an oxidizing reagent was unsatisfactory in increasing the yield of **4a** (entry 17). The structures of **3a** and **4a** were determined by analysis of their spectral data and comparison with the reported compound.[17]

Under the optimized conditions, the substrate scope and generality for the construction of various polyfunctionalized arylazopyrazoles were examined using a variety of β-ketoesters and arylhydrazines. Table 2 lists the results. Reactions of

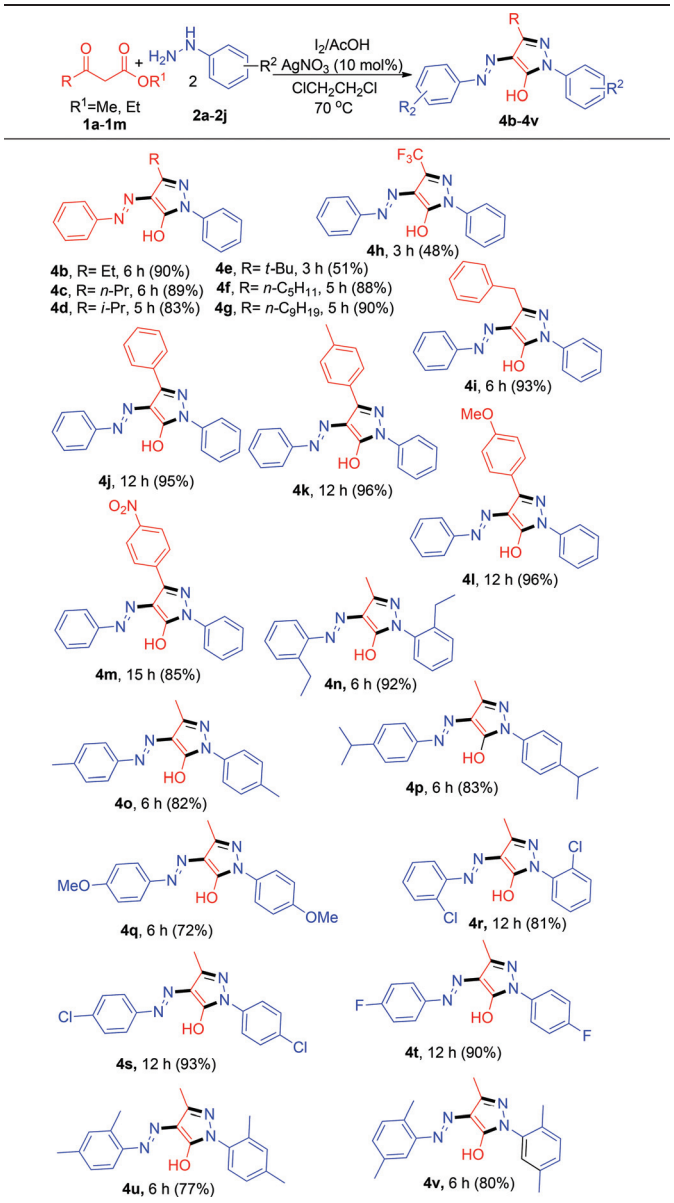
Table 1 Optimization of the reaction conditions[a]



Entry	Reagent	Catalyst	Solvent	Time (h)	Yield[b] (%) 3a	4a
1	—	—	CH_3CN	12	53	0[c]
2	—	AgOTf (10 mol%)	CH_3CN	12	65	5
3	I_2	—	CH_3CN	12	90	5
4	I_2/AcOH	—	CH_3CN	12	50	45
5	I_2/AcOH	AgOTf (10 mol%)	CH_3CN	12	0	76
6	I_2/AcOH	AgOAc (10 mol%)	CH_3CN	12	0	79
7	I_2/AcOH	$AgNO_3$ (10 mol%)	CH_3CN	6	0	81
8	I_2/AcOH	Ag_2O (10 mol%)	CH_3CN	12	0	54[c]
9	I_2/AcOH	Ag_2CO_3 (10 mol%)	CH_3CN	12	23	75
10	I_2/AcOH	$AgNO_3$ (10 mol%)	Benzene	24	0	53
11	I_2/AcOH	$AgNO_3$ (10 mol%)	THF	12	0	78
12	I_2/AcOH	$AgNO_3$ (10 mol%)	$ClCH_2CH_2Cl$	6	0	**85**
13	I_2/AcOH	$AgNO_3$ (10 mol%)	MeOH	12	0	79
14	I_2/AcOH	$AgNO_3$ (10 mol%)	H_2O	24	0	40[c]
15	NBS/AcOH	$AgNO_3$ (10 mol%)	$ClCH_2CH_2Cl$	24	0	60[c]
16	NCS/AcOH	$AgNO_3$ (10 mol%)	$ClCH_2CH_2Cl$	24	52	Trace
17	IBX	$AgNO_3$ (10 mol%)	$ClCH_2CH_2Cl$	24	0	17[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.2 mmol), reagent (1 equiv.), catalyst (10 mol%), solvent (3.0 mL) at 70 °C. [b] Yield of the isolated products **3a** and **4a** after column chromatography. [c] Incomplete reaction.

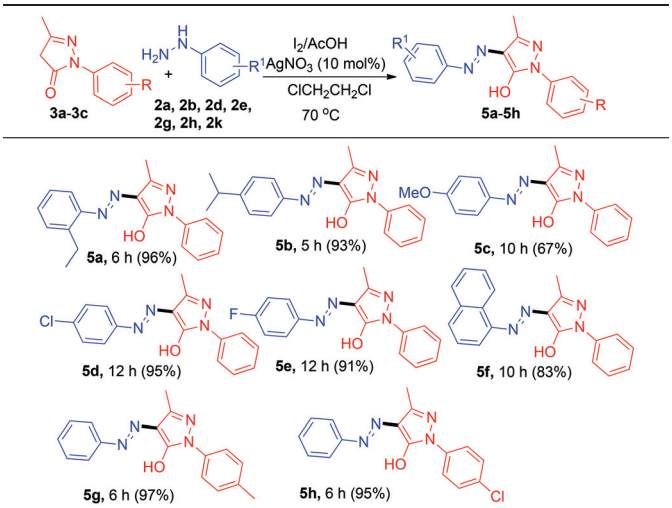
Table 2 Scope of ketoesters **1a–1m** and arylhydrazines **2a–2j** for the construction of arylazopyrazoles **4b–4v**

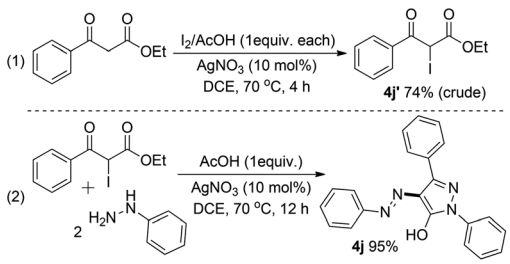


β-ketoesters bearing alkyl groups on the β-carbon were first examined. The treatment of ethyl 3-oxopentanoate (**1b**), ethyl 3-oxohexanoate (**1c**), methyl 4-methyl-3-oxopentanoate (**1d**), or ethyl 4,4-dimethyl-3-oxopentanoate (**1e**) with phenylhydrazine for 3–6 h provided the desired products **4b–4e** in 90, 89, 83, and 51% yield, respectively. The bulky group in the β-ketoesters reduces the reactivity with phenylhydrazine to give a low yield of arylazopyrazole (**4e**), possibly due to the steric hindrance. With an iodine-mediated reaction of β-ketoesters such as methyl 3-oxooctanoate (**1f**) and methyl 3-oxododecanoate (**1g**) bearing a long chain on the β-carbon with phenylhydrazine, the desired products **4f** and **4g** were isolated in 88 and 90% yields. Furthermore, β-ketoesters **1h** and **1i** containing a CF_3 or benzyl group on the β-carbon provided the desired products **4h** and **4i** in 48 and 93% yield, respectively. The additional substituent effect of phenyl and aryl on the β-carbon was next examined. A reaction of ethyl 3-oxo-3-phenylpropanoate (**1j**) with phenylhydrazine (**2a**) for 12 h afforded **4j** in 95% yield. Both β-ketoesters **1k** and **1l** bearing electron donating groups (4-Me or 4-OMe) and **1m** bearing an electron-withdrawing group (4-NO_2) were well tolerated to provide the corresponding products **4k–4m** in 96, 96, and 85% yield, respectively. Further reactions using various arylhydrazines were also successful. Diverse arylhydrazines **2b–2e** bearing electron-donating groups, such as 2-ethyl, 4-methyl, 4-isopropyl, and 4-methoxy, underwent reactions with ethyl 3-oxobutanoate (**1a**) and afforded the desired products **4n–4q** in 72–92% yield. Arylhydrazines **2f–2h** with electron-withdrawing groups, such as 2-chloro, 4-chloro, and 4-fluoro, were also suitable for the construction of the corresponding arylazopyrazoles **4r–4t** in 81, 93, and 90% yield, respectively. In addition, arylhydrazines **2i** and **2j** bearing two electron-donating groups on the benzene ring of phenylhydrazine reacted well with **1a** to afford products **4u** and **4v** in 77 and 80% yield, respectively.

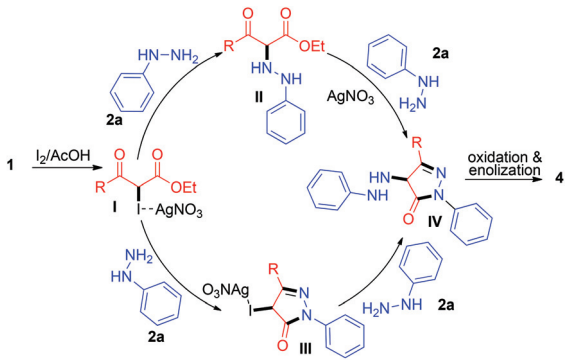
Considering the generality for the synthesis of arylazopyrazoles using various β-ketoesters, this study has examined the possibility of using 2-arylpyrazol-3-ones (Table 3). A reaction of **3a** with arylhydrazines **2b**, **2d**, and **2e** bearing electron-donating groups on the benzene ring provided the desired products **5a–5c** in 96, 93, and 67% yield, respectively, whereas treatment with arylhydrazines **2g** and **2h** bearing electron-withdrawing groups afforded products **5d** and **5e** in 95 and 91% yield, respectively. With an iodine-promoted reaction of **3a** with 1-naphthalenylhydrazine (**2k**), product **5f** was isolated in 83% yield. A combination of **3b** or **3c** with phenylhydrazine (**2a**) provided the corresponding products **5g** and **5h** in 97 and 95% yield, respectively. The arylazopyrazoles synthesized in this way contained two different hydrazine units in the same molecule. Thus the desired arylazopyrazoles can be synthesized by judicious selection of arylpyrazol-3-ones and arylhydrazines.

Table 3 Scope of selected arylpyrazol-3-ones **3a–3c** for the construction of polyfunctionalized arylazopyrazoles **5a–5h**





Scheme 3 Mechanistic investigation.



Scheme 4 Proposed mechanism for the formation of **4**.

To gain insight into the mechanism, control experiments were carried out (Scheme 3). The reaction of ethyl benzoylacetate with iodine under acidic conditions in the absence of phenylhydrazine for 4 h afforded the corresponding α-iodinated intermediate **4j′** in 74% crude yield (eqn (1), Scheme 3) (see details in the ESI†). Our attempt to isolate such an intermediate as a pure compound encountered with frequent failures regarding instability with column chromatography. An additional reaction of the crude mixture **4j′** with 2.2 equivalents of phenylhydrazine in the absence of iodine provided the product **4j** in 95% yield (eqn (2), Scheme 3). Based on control experiments and the synthesized products, a mechanism for the formation of **4** is depicted in Scheme 4. In acidic medium, β-ketoester **1** first undergoes *in situ* iodination to give α-iodo-β-ketoester (**I**),[18] which then reacts with two equivalents of phenylhydrazine to give another intermediate **IV** *via* two different intermediates **II** and **III**. Oxidation of **IV** followed by subsequent enolization in the presence of a silver catalyst would lead to the final product **4**.[17]

Conclusions

In summary, highly functionalized arylazopyrazoles were synthesized by an iodine-mediated reaction of β-ketoesters and arylhydrazines in the presence of $AgNO_3$ as a one-pot procedure. This synthetic protocol includes *in situ* α-iodination, pyrazol-3-one formation, substitution with a nitrogen nucleophile, oxidation and enolization. In addition, this protocol allowed the synthesis of a range of arylazopyrazoles bearing two different arylhydrazine units from 2-arylpyrazol-3-ones. The synthesized compounds can be expected to be widely used for the evaluation of their biological activities and photoswitch applications.

Experimental

General procedure for synthesis of arylazopyrazoles from β-ketoesters

To a solution of β-ketoester (0.5 mmol) and arylhydrazine (1.2 mmol) in 1,2-dichloroethane (3.0 mL) were added I_2 (126 mg, 0.25 mmol), acetic acid (0.03 mL, 0.5 mmol) and $AgNO_3$ (8 mg, 10 mol%) and the reaction mixture was heated at 70 °C under a nitrogen atmosphere until the completion of reaction as indicated by TLC. The volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 30 : 1) to give the desired arylazopyrazoles.

3-Methyl-1-phenyl-4-(phenyldiazenyl)-1*H*-pyrazol-5-ol (4a).[17] Orange solid (118 mg, 85%); mp 130–132 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 13.54 (s, 1H), 7.94 (d, J = 7.8 Hz, 2H), 7.42–7.37 (m, 6H), 7.19–7.16 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.69, 148.48, 141.07, 137.99, 129.58, 128.84, 128.43, 125.71, 125.05, 118.46, 115.73, 11.72.

General procedure for synthesis of arylazopyrazoles from arylpyrazol-3-ones

To a solution of 5-methyl-2-aryl-2,4-dihydro-3*H*-pyrazol-3-one (0.5 mmol) and arylhydrazine (0.6 mmol) in 1,2-dichlroethane (3.0 mL) were added I_2 (126 mg, 0.25 mmol), acetic acid (0.03 mL, 0.5 mmol) and $AgNO_3$ (8 mg, 10 mol%) and the reaction mixture was heated at 70 °C under a nitrogen atmosphere until the completion of reaction as indicated by TLC. The volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 30 : 1) to give the desired products.

4-[(2-Ethylphenyl)diazenyl]-3-methyl-1-phenyl-1*H*-pyrazol-5-ol (5a).[17] Orange solid (146 mg, 96%); mp 107–109 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 13.85 (s, 1H), 7.95–7.93 (m, 2H), 7.79 (d, J = 7.8 Hz, 1H), 7.43–7.40 (m, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.23 (d, J = 7.2 Hz, 1H), 7.20–7.18 (m, 1H), 7.15 (td, J = 7.2, 0.6 Hz, 1H), 2.77 (q, J = 7.2 Hz, 2H), 2.37 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.92, 148.50, 138.67, 138.00, 131.34, 129.15, 128.93, 127.40, 125.81, 125.18, 118.79, 114.79, 23.69, 13.82, 11.81.

Acknowledgements

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