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Iodine-promoted five-component reaction using fragment assembly strategy to construct dihydrooxepines

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ABSTRACT

An iodine-promoted fragment assembly strategy for the synthesis of fused heterocycles has been established. It provides an efficient route to construct pyrazolone-oxepine-pyrazoles from phenylhydrazines, aryl methyl ketones and acetoacetate esters. Notably, acetoacetate esters play two distinct pivotal roles in the five-component reaction by realizing the unique reactivities of methyl, methylene and carbonyl groups to construct 3-methyl-5-pyrazolone skeletons and by the reaction of methyl and carbonyl groups to form a C (sp3)-O bond.

1. Introduction

Multi-component reactions (MCRs) are powerful tools for rapidly increasing molecular complexity and diversity, and have a rich history [1]. In particular, MCRs as novel strategies for quickly assembling small molecules to construct molecular libraries have received widespread attention and undergone rapid development because of the emergence of molecular biology and high-throughput biological screening for drug discovery [1,2]. However, the majority of developed MCRs, including named reactions, are limited to three [3]-or four-component [4] reactions. MCRs involving five or more components have been a long-standing challenge in organic synthesis owing to the difficulty in controlling the reactivity, selectivity, and compatibility with increasing number of reaction components. Recently, pyrazolones and their derivatives have emerged as an important family of five-membered heterocycles, and they are frequently found in natural products, biologically active molecules and pharmaceutical agents [5]. Therefore, several methods for the synthesis of pyrazolone derivatives have been intensively investigated to diversify the pyrazolone-based structures available for potential medicinal research. Among these elegant methods, using 3-methyl-pyrazolin-5-ones as substrates is especially appealing, because these compounds contain a diverse array of reactive centers [6]. The main strategy is using 3-methyl-pyrazolin-5-ones as nucleophiles to build spiropyrazolones or functionalize pyrazolones via formal cycloaddition or nucleophilic addition reactions (Scheme 1a) [7,8]. Furthermore, considerable attention has been paid to the development of cascade reactions to construct fused pyrazole derivatives by exploiting the binucleophilic nature of pyrazolones via enol tautomerism (Scheme 1b) [9]. Recently, the prior preparation of unsaturated pyrazolones has been exploited to develop tandem reactions to construct heterocycles (Scheme 1c) [10]. These elegant approaches mainly involve methylene and carbonyl groups acting as O-nucleophiles.

However, directly employing the methyl group of pyrazolone formed in-situ has not yet to be exploited in organic synthesis. Furthermore, implementing identical molecules that can exhibit distinctly different reaction selectivities simultaneously in the same chemical system via a fragment assembly strategy remains a challenge and attractive prospect. To date, examples of methyl, methylene and carbonyl groups in acetoacetate esters being used to directly construct C–O bonds for the synthesis of dihydrooxepine rings have not been reported. Owing to our interest in the further development of multi-component reactions and the construction of medium-sized ring compounds, we now report an iodine-promoted five-component fragment assembly strategy for the synthesis of multi-heterocyclic compounds, in which acetoacetate

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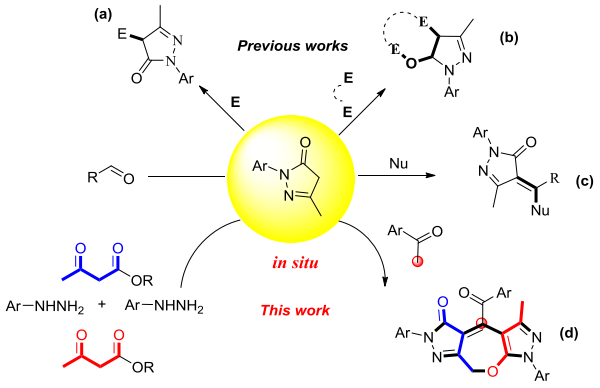


Scheme 1. Applications of pyrazolones and their derivatives in organic synthesis.

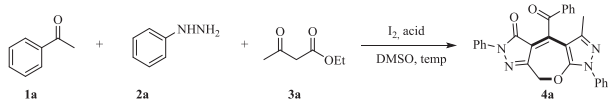
esters not only react with phenylhydrazines to forge pyrazolones, but also exhibit distinctly different reaction selectivity to construct C–O bonds for the synthesis of fused oxepine derivatives.

2. Results and discussion

Our initial attempt focused on the model reaction of acetophenone (**1a**), phenylhydrazine (**2a**), and ethyl acetoacetate (**3a**) in the presence of molecular iodine at 100 °C. The desired product 2,3-dihydrooxepine product was obtained in 25% yield when the **1a**/**2a**/**3a** molar ratios were 1:1.5:2 (Table S1, entry 1). Subsequent studies showed that a **1a**/**2a**/**3a** molar ratio of 1:2:2 increased the yield of **4a** to 30% (Table 1, entry 1). Different temperatures were also applied to this multi-component reaction, with 140 °C found to give the best yield (Table 1, entries 2–4).

Next, a series of Brønsted and Lewis acids were screened as additives for the reaction, with TfOH determined to be the optimal additive for the five-component reaction (Table 1, entries 5–10). The effect of different amounts of TfOH on the outcome of the reaction was also investigated. The results showed that the amount of TfOH had a prominent effect on the yield (Table 1, entry 11). Finally, we tested the effect of different amounts of iodine on the reaction outcome. The reaction proceeded smoothly when the amount of iodine was decreased to 50 mmol % (Table 1, entry 12). To our surprise, the optimum yield was still obtained when the amount of iodine was further decreased to 10 mmol % (Table 1, entry 13). However, the reaction did not proceed without iodine (Table 1, entry 14), which confirmed that iodine played a critical role in this transformation.

Table 1
Optimization of the reaction conditions[a].

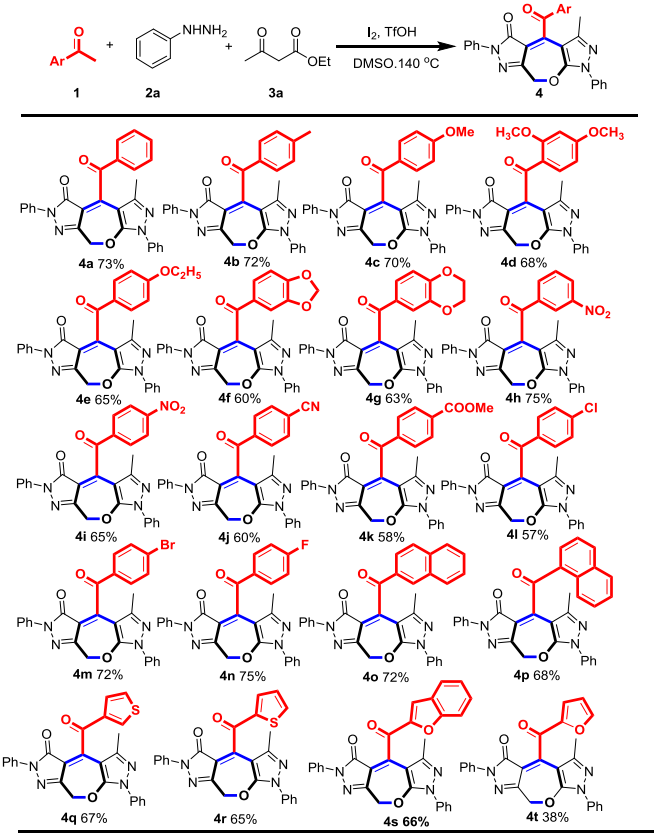


entry	temp (°C)	I_2 (equiv)	additive	yield/%[b] (time/h)
1	100	1.0		30 (24 h)
2	110	1.0		35 (24 h)
3	130	1.0		42 (12 h)
4	140	1.0		46 (12 h)
5	140	1.0	$TsOH·H_2O$	52 (7 h)
6	140	1.0	$FeCl_3$	21 (12 h)
7	140	1.0	$ZnCl_2$	47 (7 h)
8	140	1.0	$Cu(OTf)_2$	54 (7 h)
9	140	1.0	CF_3SO_3H	65 (7 h)
10	140	1.0	HCl	37 (12 h)
11[c]	140	1.0	CF_3SO_3H	72 (7 h)
12[c]	140	0.5	CF_3SO_3H	71 (7 h)
13[c]	140	0.1	CF_3SO_3H	73 (7 h)
14[c]	140		CF_3SO_3H	NR[d]

[a] [a]Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), **3a** (2.0 mmol), I_2, and additive (1.0 mmol) heated in DMSO (4 mL).
[b] Isolated yields.
[c] 2.5 mmol TfOH was used instead of 1.0 mmol TfOH.
[d] NR = No Reaction.

With the optimized reaction conditions in hand, we next investigated the scope of the five-component reaction. To our satisfaction, a variety of acetophenone derivatives bearing different functional groups and substitution patterns afforded the desired products in moderate to good yields (38%–75%), as shown in Scheme 2. For example, aryl methyl ketones bearing (4-H), electron-rich (4-Me, 4-OMe, 3,4-OCH_2O, 3,4-OCH_2CH_2O), and electron-deficient (3-NO_2, 4-NO_2, 4-CN, 4-COOMe) groups exhibited excellent reactivity, affording the corresponding products in moderate to good yields (58%–75%, **4a**–**4k**). The substrate was further also successfully extended to various halogenated (4-Cl, 4-Br, 4-F) substrates (57%–75%, **4l**–**4n**). Notably, 2-naphthyl methyl ketone and 1-naphthyl methyl ketone were also tolerated in this transformation (68%–72%, **4o**–**4p**). Furthermore, various heteroaryl ketones, including thienyl, benzofuryl, and furyl ketones, were found to be compatible under the optimal conditions, giving the corresponding products in moderate yields (38%–67%, **4q**–**4t**).

The scope of the study was then extended to substituted phenylhydrazines, with the results shown in Scheme 3. Various substituted phenylhydrazines were found to be compatible in the reaction. For example, electron-rich (4-CH_3) and halogen (3-Cl, and 4-Cl) groups on the phenyl rings were tolerated, affording the corresponding products in moderate to good yields (**4u**–**4y**, 35%–



Scheme 2. Scope of methyl ketones.