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Iron(III)-catalyzed Highly Efficient, One-pot Synthesis of Triazolo[1,2-*a*]indazoletriones and Spirotriazolo[1,2-*a*]indazoletetraones

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Three-component coupling (3CC) of aldehyde, 1,3-dione, and 4-phenylurazole has been achieved in the presence of 10 mol % anhydrous $FeCl_3$ in acetonitrile under reflux conditions to afford the corresponding triazolo[1,2-*a*]indazoletriones in excellent yields while the coupling of isatins with 4-phenylurazole and 1,3-diones gave the spirotriazolo[1,2-*a*]indazoletetraones under similar conditions.

Multicomponent reactions (MCRs) are highly important because of their wide range of applications in pharmaceutical chemistry for the rapid generation of structural diversity in combinatorial libraries for drug discovery.[1] MCRs are extremely convergent, producing a remarkably high increase in molecular complexity in a single-step process.[2,3] In particular, triazolo[1,2-*a*]indazoletrione, spirotriazolo[1,2-*a*]indazoletetraone, and their derivatives are important structural motifs in medicinal and pharmaceutical chemistry. They are known to exhibit promising physiological and biological properties such as anticancer and hypolipidemic,[4] anticonvulsant,[5] fungicidal activity,[6] and a catalytic role in radical polymerization.[7] These compounds are also used for the preparation of herbicides, pesticides, insecticides, and polymeric materials with unique properties such as heat-resistant coatings, and high grip ability for rubber tires and melamine resins. Triazolo[1,2-*a*]indazoletriones are present in many pharmacological agents and natural alkaloids like HSP-72 induction inhibitors (I and III) and novel microtubule assembly inhibitors, spirotryprostatin (II), as shown in Figure 1.[4b,8]

As a result, numerous approaches have been reported for the synthesis of triazolo[1,2-*a*]indazoletrione and spirotriazolo[1,2-*a*]indazoletetraone derivatives.[9] However, many of these methods often involve long reaction times, harsh reaction conditions, and expensive catalysts. Thus, there is a need to develop a simple and cost-effective method for the synthesis of triazolo-[1,2-*a*]indazoletriones and spirotriazolo[1,2-*a*]indazoletetraones.

The Lewis acid catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions are of great importance in organic synthesis because of their high reactivity, selectivity, and mild reaction conditions.[10,11] In particular, iron(III) chloride has emerged as a powerful Lewis acid to facilitate various organic transformations under mild reaction conditions.[12] Moreover, iron salts are inexpensive, easy to handle, and environmentally friendly. To the best of our knowledge, this is the first report on the synthesis of triazolo[1,2-*a*]indazoletrione and spirotriazolo[1,2-*a*]indazoletetraone derivatives using $FeCl_3$ as the catalyst via a three-component reaction.

In continuation of our interest in exploring the synthetic utility of $FeCl_3$[13] and MCRs,[14] we herein report a highly efficient three-component approach for the synthesis of triazolo[1,2-*a*]indazoletrione derivatives from 4-phenylurazole, aldehydes, and 1,3-diones using an iron(III) catalyst. In a model reaction,

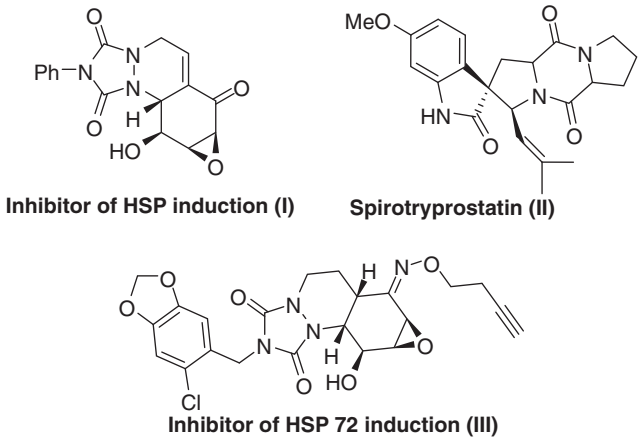


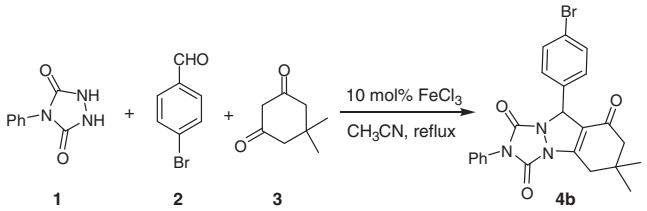
Figure 1. Biologically active urazole and spirooxindole derivatives.

Table 1. Screening of various acid catalysts and solvents in the formation of product **4b**

Entry	Acid catalyst	Mol % of the catalyst[a]	Solvent	Time /h	Yield /%[b]
a	CAN	10	CH_3CN	8.5	75
b	Phosphomolybdic acid	10	CH_3CN	8.2	80
c	Cellulose-SO_3H	10	CH_3CN	3.5	70
d	$FeCl_3$	10	THF	12.0	60
e	$FeCl_3$	10	DCE	12.0	75
f	$FeCl_3$	10	EtOH	6.5	85
g	$FeCl_3$	5	CH_3CN	5.0	78
h	$FeCl_3$	10	CH_3CN	2.0	90
i	I_2	10	CH_3CN	8.5	75
j	$In(ClO_4)_3$	10	CH_3CN	8.0	60
k	$CeCl_3 \cdot 7H_2O$/LiI	20/1.0 equiv	CH_3CN	12.0	55

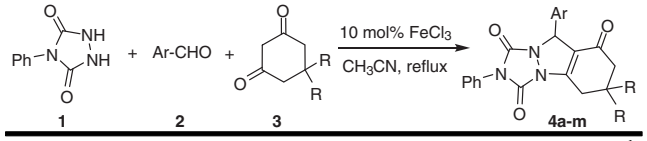
[a]The reaction was performed at 1 mmol scale at 80 °C. [b]Isolated yield.

we attempted a three-component coupling of 4-phenylurazole (**1**), 4-bromobenzaldehyde (**2**), and dimedone (**3**) in the presence of various amounts of $FeCl_3$ in acetonitrile. Initially, 5 mol % $FeCl_3$ was used to perform the reaction. However, the product **4b** was obtained in a low yield either in acetonitrile or in ethanol at room temperature even after a long reaction time (10 h). Therefore, the catalyst loading was gradually increased from 5 to 50 mol %. After several experiments, it was found that 10 mol % of $FeCl_3$ is optimal to achieve a high conversion at 80 °C (Table 1). The use of excess catalyst also did not alter either reaction time or yield. Therefore, the treatment of 4-phenylurazole (**1**) with 4-bromobenzaldehyde (**2**) and dimedone (**3**) in the presence of 10 mol % $FeCl_3$ at 80 °C in acetonitrile afforded



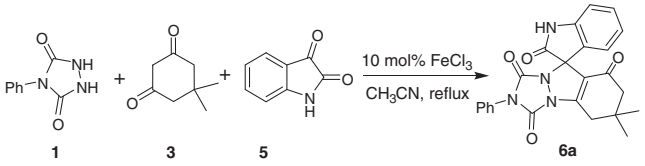
Scheme 1. Three-component coupling (3CC) of 4-phenylurazole, 4-bromobenzaldehyde, and dimedone.

Table 2. $FeCl_3$-catalyzed 3CC reaction for the synthesis of triazolo[1,2-*a*]indazoletriones



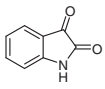
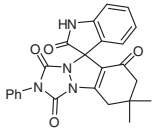
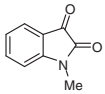
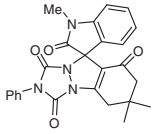
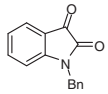
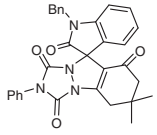
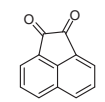
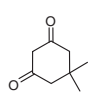
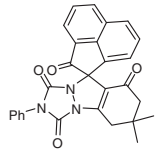
Entry	Ar	R	Product[a]	Time/min	Yield/%[b]
a	Ph	CH_3	**4a**	30	87
b	4-BrC_6H_4	CH_3	**4b**	27	90
c	4-$NO_2C_6H_4$	CH_3	**4c**	29	92
d	4-$CH_3C_6H_4$	CH_3	**4d**	30	86
e	3-$CH_3OC_6H_4$	CH_3	**4e**	35	84
f	3-$PhOC_6H_4$	CH_3	**4f**	35	82
g	3-ClC_6H_4	CH_3	**4g**	32	90
h	2-Naphthyl	CH_3	**4h**	38	86
i	4-ClC_6H_4	H	**4i**	28	93
j	3-$PhOC_6H_4$	H	**4j**	34	83
k	4-FC_6H_4	H	**4k**	40	92
l	4-$NO_2C_6H_4$	H	**4l**	35	90
m	4-$CH_3OC_6H_4$	H	**4m**	40	82

[a]All products were characterized by NMR and IR spectroscopy and mass spectroscopy. [b]Yield refers to pure products after chromatography.



Scheme 2. 3CC reaction between 4-phenylurazole, dimedone, and isatin.

Table 3. $FeCl_3$-catalyzed 3CC reaction for the synthesis of spirotriazolo[1,2-*a*]indazoletetraones

Entry	Ketone (**5**)	Diketone (**3**)	Product (**6**)[a]	Time/min	Yield/%[b]
a				90	85
b				80	91
c				75	87
d				90	82

[a]All products were characterized by NMR and IR spectroscopy and mass spectroscopy. [b]Yield refers to pure products after chromatography.

the corresponding 9-(4-bromophenyl)-6,6-dimethyl-2-phenyl-6,7-dihydro-[1,2,4]triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (**4b**) in 90% yield (Table 1 and Scheme 1).

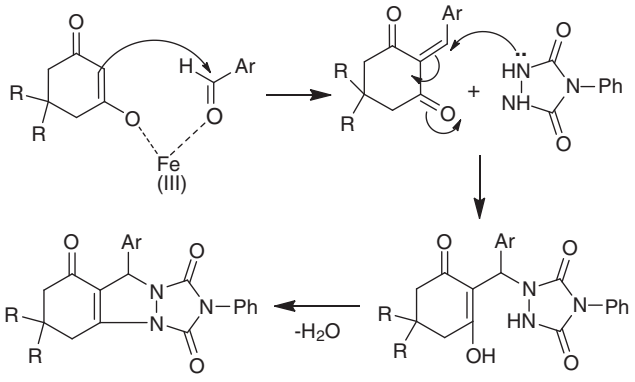
In order to realize the catalytic efficiency, we performed the above reaction with various acid catalysts such as $FeCl_3$, $CeCl_3 \cdot 7H_2O$/LiI, $In(ClO_4)_3$, iodine, ceric ammonium nitrate (CAN), heteropolyacid, and cellulose–sulfonic acid. Among these catalysts, anhydrous $FeCl_3$ was found to be more effective than others in terms of reaction time and yield (Entry h, Table 1). Next, we examined the effect of various solvents such as 1,2-dichloroethane, tetrahydrofuran, ethanol, and acetonitrile. Of these, acetonitrile appeared to give the best results (Table 1).

Inspired by the above results, we extended this method to other substrates. Interestingly, a variety of aldehydes including *ortho*-, *meta*-, and *para*-substituted benzaldehydes participated effectively in this reaction (Table 2).

As summarized in Table 2, the substituent on the aromatic ring had shown some effect on conversion. For instance, halo-substituted aromatic aldehydes gave the products in comparatively higher yields than electron-rich aldehydes such as methoxy, phenoxy, and methyl derivatives did. Remarkably, a sterically hindered 2-naphthaldehyde also afforded the product in 86% yield (Entry h, Table 2). Both dimedone and 1,3-cyclohexanedione furnished the corresponding products in excellent yields. The scope and generality of this process is illustrated in Table 2.[15] However, most of the reported Brønsted acids such as *p*-TSA, nanosilica–SO_3H sulfamic acid, and AlKIT-5 are successful only with aldehydes not with ketones. Although PEG–SO_3H has successfully been utilized to catalyze the reaction with isatin derivatives, the catalyst is not readily available. Notably, $FeCl_3$ works with both aldehydes and ketones in short reaction times. Therefore, the present method is advantageous over Brønsted acids.

Encouraged by the results obtained with aldehydes, we turned our attention toward ketones. Accordingly, the coupling of 4-phenylurazole (**1**) and dimedone (**3**) with isatin (**5**) afforded the spirotriazolo[1,2-*a*]indazoletetraone in 85% yield under similar conditions (Scheme 2).

Other isatin derivatives such as *N*-methyl and *N*-benzyl derivatives also participated well in this reaction (Entries b and c, Table 3). Interestingly, acenaphthoquinone also gave the desired product in 85% yield (Entry d, Table 3). The results obtained with ketones are presented in Table 3.[15]



Scheme 3. A plausible reaction pathway.

The reaction was proposed to proceed via the formation of the enone from aldehyde and 1,3-diketone. This is followed by the attack of 4-phenylurazole on the enone, and a subsequent cyclodehydration would result in the formation of the desired product, as depicted in Scheme 3.

In summary, we have developed a highly efficient method for the synthesis of triazolo[1,2-*a*]indazoletrione and spirotriazolo[1,2-*a*]indazoletetraone derivatives through the coupling of aldehyde or ketone with 1,3-dione and 4-phenylurazole using a catalytic amount of $FeCl_3$. The use of $FeCl_3$ makes this method quite simple, more convenient, and cost-effective, and thus, it provides an easy access to triazolo[1,2-*a*]indazole derivatives in a single-step process.

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