



A consecutive one-pot two-step approach to trifluoromethylated pyrazolo [4',3':5,6]pyrano[2,3-b]indoles promoted by molecular iodine

Yingjun Zhu^a, Fanhui Chen^a, Yidi Zhou^a, Zhangping Kang^a, Min Zhang^a, Hongmei Deng^c, Liping Song^{a,b,*}

^a Department of Chemistry, School of Science, Shanghai University, No. 99, Shangda Road, Shanghai 200444, China

^b Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

^c Laboratory for Microstructures, Shanghai University, Shanghai, China

ARTICLE INFO

Keywords:

Fluorinated poly-heterocycle
Multicomponent reactions
Molecular iodine
Annulation
2-Indolinone

ABSTRACT

An one-pot two-step three-component reaction of 2-indolinone, aromatic aldehydes and 1-aryl-3-trifluoromethyl-5-pyrazolone afforded trifluoromethylated poly-heterocyclic compounds containing pyrazolo [4',3':5,6]pyrano[2,3-b]indole skeleton. This atom economic and facile manipulative reaction involved initial treatment of three-component reaction mixtures with molecular iodine, followed by intramolecular annulation reaction with POCl₃ in one-pot manner without isolation. Compared with the step-wise reactions, a more consecutive approach to trifluoromethylated pyrazolo[4',3':5,6]pyrano[2,3-b]indoles was achieved.

1. Introduction

Poly-heterocyclic compounds might be used as potential drug candidates because they might be capable to exhibit kinds of biological activities of their parent compounds [1]. As a result, the synthesis of poly-heterocyclic compounds by one-pot, multi-component reactions (MCRs) has attracted significant interest in recent years [2].

Pyrazole framework is a well-known heterocyclic moiety, which has been considered for reevaluation in the clinic as a potential cytotoxic agent [3]. Further literature survey reveals that pyrazoline and pyrazole are important structural fragments of many bioactive compounds, which exhibit a wide spectrum of important bioactivities such as anti-proliferative, antitumor, antibacterial, antifungal, anti-angiogenic properties [4–6].

From another aspect, the indole skeleton represents an important structural constituent in many natural products, displaying a wide variety of biological and pharmaceutical activities [7–10]. Particularly, a very recent study has revealed that compounds with indole ring always show much higher tumor specificity (TS) values than those with another heterocycles [11]. For this viewpoint, the functionalization of indoles has been extensively studied [12,13]. Thus, it is not surprising that the incorporation of indole ring into poly-heterocyclic structures might result in the produce of new hybrid molecules, which is relevant for the identification of novel potential biologically active compounds [2].

It is well known that the introduction of trifluoromethyl groups into

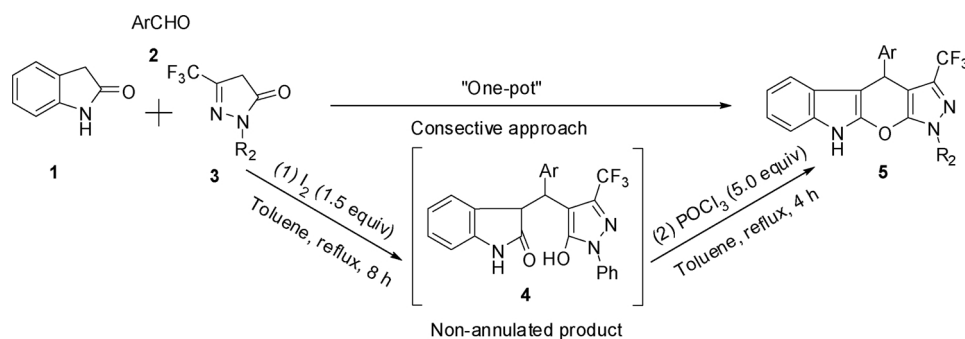
heterocyclic compounds can bring about remarkable changes in the physical, chemical, and biological properties [14]. For instance, the introduction of trifluoromethyl group to molecules can change the biological properties used in medicinal chemistry for the design of new drugs [15]. Therefore, the synthesis of fluorine-containing poly-heterocyclic compounds is particularly important.

The reactions of 2-indolinone and aromatic aldehydes were widely explored [16,17]. Jahng and co-workers reported that 2-indolinone could participate in the cyclization reaction to produce the tryptanthrin [18]. However, the one-pot MCRs cyclization reactions were considerably less investigated. In continuation of our ongoing exploration to the synthesis of fluorine-containing poly-heterocycles via one-pot, MCRs [19], herein, we reported a one-pot, two-step reactions for synthesis of trifluoromethylated pyrazolo[4',3':5,6]pyrano[2,3-b]indole derivatives by the reaction of 2-indolinone (1), aromatic aldehydes (2) with 1-aryl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one (3) promoted by molecular iodine.

2. Results and discussion

Initially, we expected that the trifluoromethylated pyrazolo [4',3':5,6]pyrano[2,3-b] indole derivatives 5 might be straightforwardly formed via an one-pot three-component condensation reaction of 2-indolinone (1) and aromatic aldehydes (2) with 1-aryl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one (3) in the presence of appropriate catalysts (Scheme 1). But unfortunately, no reaction occurred when this

* Corresponding author at: Department of Chemistry, School of Science, Shanghai University, No. 99, Shangda Road, Shanghai 200444, China.
E-mail address: lpson@shu.edu.cn (L. Song).



Scheme 1. Synthesis of trifluoromethylated pyrazolo[4',3':5,6]pyrano[2,3-b]indoles.

Table 1
Optimization of one-pot reaction for preparation of **4**^a.

Entry	Promoter/ equiv.	Solvent	Temperature/°C	Time/h	Yields of 4 (%) ^b
1	I ₂ /1.0	EtOH	reflux	8	N.R
2	I ₂ /1.0	MeOH	reflux	8	N.R
3	I ₂ /1.0	Dioxane	reflux	8	N.R
4	I ₂ /1.0	Acetone	reflux	8	N.R
5	I ₂ /1.0	Toluene	r.t.	8	N.R
6	I ₂ /1.0	Toluene	80	8	65
7	I ₂ /1.0	Toluene	reflux	8	69
8	I ₂ /0.5	Toluene	reflux	8	51
9	I ₂ /1.5	Toluene	reflux	8	78
10	I ₂ /2.0	Toluene	reflux	8	78

^a Reaction conditions: **1** (1.2 mmol), **2** (1.2 mmol), **3** (1.0 mmol), solvent: 10.0 mL.

^b Isolated yield.

one-pot three-component reaction was carried out in the presence of a catalytic amount of conventionally used either bases or acids under various reaction conditions. To our delight, when the catalyst was switched from commonly used either acids or bases to molecular iodine in refluxing toluene (Entry 8, Table 1), TLC analysis showed that the reaction proceeded smoothly and general work-up afforded the non-annulated product **4** in 51% yield. To further optimize the reaction conditions, several parameters such as solvent, the amount of molecular iodine and reaction temperature were optimized to improve the yields (Table 1). It was found that no desired product **4** was formed when the reaction was carried out in the commonly used solvent such as EtOH, MeOH, dioxane or acetone in the presence of stoichiometric amount of molecular iodine (entries 1–4, Table 1). It should be noted that: although the reaction could take place in the presence of a catalytic amount of molecular iodine, increasing the amount of molecular iodine had significant effects on the reaction yields (Entries 7–9, Table 1). The best result was obtained when the amount of molecular iodine was increased to 1.5 equivalents, but further increasing the amount of molecular iodine to 2.0 equivalents did not result in an improved yield (entries 10, Table 1). From this viewpoint, molecular iodine, acted as a promoter, rather than as a catalyst, played a unique role in this conversion. Finally, the reaction temperature affecting the reaction efficiency was screened as well. Raising the reaction temperature from 80 °C to refluxing in toluene (110 °C) led to an increased yield (Table 1, entries 5–7, Table 1), whereas no product **4** was formed when the reaction was carried out at room temperature (entry 5, Table 1).

Having established the optimal conditions for preparation of products **4**, the annulation reaction of product **4** by way of intramolecular dehydration was studied. It is well known that *p*-TSA, P₂O₅, POCl₃ or

Table 2
Optimization of dehydration reaction of product **4**^a.

Entry	Dehydrating reagent/equiv.	Solvent	Time/h	Yield of 5 (%) ^b
1	<i>p</i> -TSA/1.0	CHCl ₃	4	N.R
2	P ₂ O ₅ /1.0	CHCl ₃	4	N.R
3	H ₂ SO ₄ /1.0	CHCl ₃	4	N.R
4	POCl ₃ /1.0	CHCl ₃	4	trace
4	POCl ₃ /5.0	DCE	4	90
5	POCl ₃ /5.0	Toluene	4	89
6	POCl ₃ /3.0	Toluene	4	70

^a Reaction conditions: **4** (0.5 mmol), solvent: 7.0 mL, refluxing.

^b Isolated yield.

H₂SO₄ all are efficient cyclization reagents and dehydrating reagents. Furthermore, POCl₃ are found to have wide applicability in preparing oxy-heterocyclic compounds [20,21]. Inspired by the above precedents, we performed the annulation reaction of product **4**. As shown in Table 2, no corresponding annulated product **5** was obtained when the reaction was carried out in the solvent of trichloromethane using various dehydrating reagents (entries 1–4, Table 2). Switching the solvent to dichloroethane afforded the desired annulated product **5** in 90% yield by treatment of product **4** with an excess amount of POCl₃/pyridine. Meanwhile, a similar reaction result was observed when the reaction was performed in toluene as solvent, and compatible product yield was obtained (entry 5, Table 2). Note that the yield of the reaction was obviously decreased by reducing the quantity of dehydrating reagent (entry 6, Table 2).

Taking into consideration the fact that the above two reactions were also carried out in the same solvent, we wonder whether the step-wise reactions would be carried out in one-pot two-step manner. To our delight, a more consecutive approach to the corresponding annulated products **5** was achieved by initial treatment of reaction mixtures with molecular iodine, followed by POCl₃/pyridine in one-pot process without purification and isolation. For example, after the initial one-pot three-component reaction of 2-indolinone (**1**), benzaldehyde (**2a**) with 1-phenyl-3-(trifluoromethyl)-5-pyrazolone (**3**) promoted by molecular iodine in refluxing toluene for 8 h, the dehydrating reagent POCl₃/pyridine was added drop-wise to the reaction mixture. After the resulting mixture was refluxed for another 4 h, the completion of the reaction was observed by TLC analysis. This one-pot two-step three-component reaction resulted in the formation of the corresponding annulated product **5a** in 71% yield.

Under the above identified reaction conditions, we investigated the scope and limitation of this one-pot two steps reaction with a variety of aromatic aldehydes (**2**) and 1-aryl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**3**). As shown in Table 3, generally, the aromatic aldehydes

Download English Version:

<https://daneshyari.com/en/article/7752337>

Download Persian Version:

<https://daneshyari.com/article/7752337>

[Daneshyari.com](https://daneshyari.com)