Tetrakis(acetonitrile)copper(I) Hexafluorophosphate as an Efficient Catalyst for the Synthesis of Triazolo[1,2-a]indazole-1,3,8-trione and 2*H*-indazolo[2,1-b]phthalazine-trione Derivatives

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Abstract: Tetrakis(acetonitrile)copper(I) hexafluorophosphate, $[Cu(CH_3CN)_4]PF_6$, was explored as an efficient catalyst to promote the three-component reaction of aryl aldehydes, dimedone and urazole or phthalhydrazide to afford the corresponding triazolo[1,2-a]indazole-1,3,8-trione and 2*H*-indazolo[2,1-b]phthalazine-trione derivatives respectively in high yields. The reactions were conducted at 80-100 ºC under solvent-free conditions. The catalyst was easily prepared from available and inexpensive materials and was quantitatively recovered from the reaction by simple filtration and reused for a number of cycles with almost consistent activity.

Keywords: 2*H*-Indazolo[2,1-b]phthalazine-trione, dimedone, phthalhydrazide, tetrakis(acetonitrile)copper(I)hexafluorophosphate, triazolo[1,2-a]indazole-1,3,8-trione, urazole.

INTRODUCTION

The developments of multi-component reactions (MCRs) have attracted much attention from the vantage point of combinatorial and medicinal chemistry [1]. Generally, the MCR strategy affords savings in reaction time and effort, and presents significant advantages over conventional multi-stage reactions in several aspects, such as variable and high bond forming efficiency. With a small set of starting materials, very large libraries can be developed within a short time, which can apply to research on medicinal chemistry.

Heterocyclic compounds occur very widely in nature and many of them play vital role in life. An important class of these compounds belongs to nitrogen-containing heterocyclic molecules constituting the largest portion of chemical entities which are part of many natural products, fine chemicals and biologically active pharmaceuticals vital for enhancing the quality of life [2-4]. Among the various products obtained from multi-component processes, triazolo[1,2-a]indazole-1,3,8-triones [5] are known as an important class of nitrogen-containing heterocyclic compounds which exhibit high biological activities [6, 7]. In addition, heterocyclic compounds containing 1,2,4-triazolidine-3,5-dione unit known as urazoles, also exhibit biological activities as anti-convulsant and fungicidal agents [8-10]. Moreover, phthalazine derivatives, constituting a bridgehead hydrazine are reported to possessing multiplicity of pharmacological properties including anti-convulsant [11], vasorelaxant [12], and cardiotonic [13] activities. Albeit there are several methods available for the synthesis of different phthalazine derivatives [14, 15], their broad range of utility has accentuated the need to develop more improved synthetic approaches for scaffold manipulation of N-heterocycles containing phthalazine moiety. On the other hand, pyrazoles are another important class of N-heterocyclic compounds of diverse structures with a wide range of interesting biological properties, such as analgesic, anti-pyretic, anti-bacterial, anti-inflammatory, anti-diabetic and psychoanaleptic activities [16].

We have developed a convenient one-pot three component cyclocondensation reaction between phthalhydrazide, or 4-phenylurazole with aromatic aldehydes, and dimedone for the preparation of 2*H*-indazolo[2,1-b]phthalazine-trione and triazolo[1,2-a]indazole-1,3,8-trione of potential synthetic and pharmacological interests. Solvent-free conditions, good yields of the products, recyclability of the catalyst and the use of simple and readily available starting materials are the main advantages of this method.

RESULTS AND DISCUSSION

In continuation of our efforts to develop newer and more benign methods for the synthesis of various heterocyclic compounds [17-20], we now report a simple and efficient route for the synthesis of 2*H*-indazolo[2,1- b]phthalazine-trione (5) and triazolo[1,2-a]indazole-1,3,8-trione (6) derivatives using aryl aldehydes (1), dimedone and phthalhydrazide (3) or urazole (4) under the catalytic effect of tetrakis(acetonitrile)copper(I) hexafluorophosphate and solvent-free conditions (Scheme **1**).

In order to establish the conditions for the titled reactions, we preliminary examined the model condensation reaction between 4-chlorobenzaldehyde, dimedone and phthalhydrazide as test compounds. The effects of catalyst were studied using various catalysts such as $FeCl_3.SiO_2$ and

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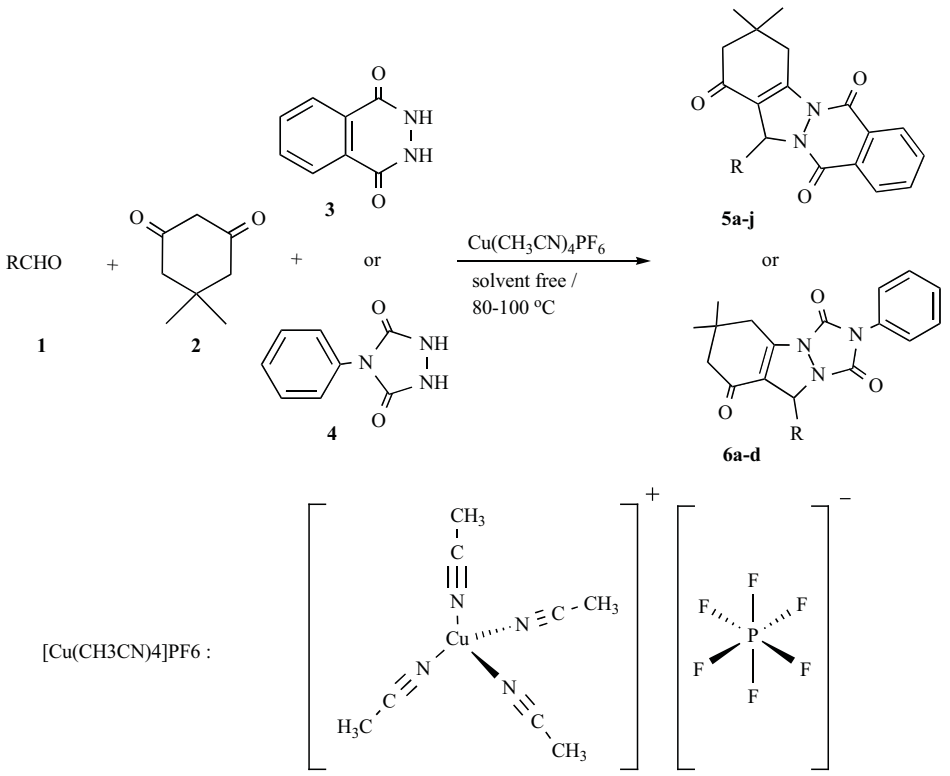


Scheme 1.

$ZnCl_2.SiO_2$ under solvent-free conditions (Table **1**). As seen in this Table **1**, it was noticed that, the reaction worked out best under solvent-free conditions using a (15 mol %) $[Cu(CH_3CN)_4]PF_6$ as catalyst. An increase in the catalyst to 20 mol % showed no substantial improvement in the yield.

This encouraged us to study the scope of the reaction under the optimized reaction parameters in the presence of 15 mol % of catalyst under solvent-free condition. The results of using $Cu(CH_3CN)_4PF_6$ as a catalyst for synthesis of products 5a-j and 6a-d are summarized in Table **2**. The products 5a-j and 6a-d were characterized on the basis of their physical and spectral (IR and ^{1}H NMR) data which were in accord with those reported in the literature [21-26].

$Cu(CH_3CN)_4PF_6$ is a free-flowing, white, microcrystalline powder that does not darken on long-term storage in an inert atmosphere. Exposure to air for longer than about 1 h results in minor surface oxidation due to the slightly hygroscopic nature of the complex. The complex is moderately soluble in polar solvents and is remarkably stable to air oxidation in CH_3CN solution.

As shown in Scheme **2**, these reactions seem to proceed through the formation of the intermediate (I) resulted from the tetrakis(acetonitrile)copper(I) hexafluorophosphate-catalyzed condensation of aldehydes 1 with dimedone 2, which undergoes subsequent Michael addition with phthalhydrazide 3 or urazole 4 to provide the intermediates (II) and (III) respectively. The successive cyclocondensation and dehydration of these intermediates occur to furnish the corresponding 2*H*-indazolo[2,1-b]phthalazine-triones 5 and triazolo[1,2-a]indazole-1,3,8-triones 6 respectively.

EXPERIMENTAL

Chemicals used in this work were purchased from Fluka and Merk chemical companies and used without purification. IR spectra were recorded on a Shimadzu 435-U-04 FT

Table 1. Optimization of the Reaction Conditions for the Reaction of 4-chlorobenzaldehyde, Dimedone and Phthalhydrazide

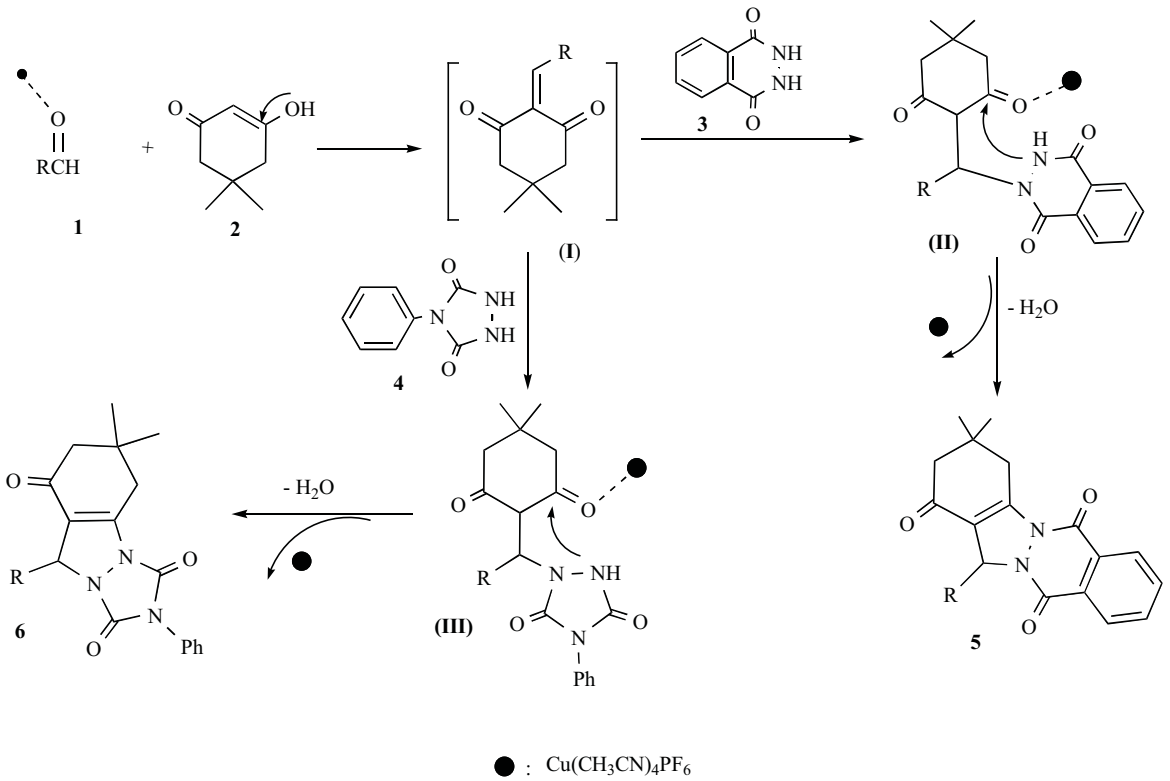
Entry	Catalyst (mol%)	Time (min)	Yield (%)[a]
1	$[Cu(CH_3CN)_4]PF_6$ (5)	10	48
2	$[Cu(CH_3CN)_4]PF_6$ (10)	10	73
3	$[Cu(CH_3CN)_4]PF_6$ (15)	10	90
4	$[Cu(CH_3CN)_4]PF_6$ (20)	10	91
5	$ZnCl_2.SiO2$ (15)	10	68
6	$FeCl_3.SiO_2$ (15)	10	72

[a]Isolated Yield.

Table 2. Synthesis of Triazolo[1,2-a]indazole-1,3,8-trione and 2*H*-indazolo[2,1-b]phthalazine-trione Derivatives Catalyzed by Tetrakis(acetonitrile)copper(I) Hexafluorophosphate as Catalyst Under Solvent-Free Conditions

Entry	R	Product[a]	Time (min)	Yield[b] (%)	M.p (°C)
1	Ph	**5a**	10	86	204-206
2	4-ClC_6H_4	**5b**	10	90	261-263
3	3-$NO_2C_6H_4$	**5c**	10	85	272-274
4	3-ClC_6H_4	**5d**	10	88	205-207
5	4-FC_6H_4	**5e**	10	92	219-221
6	4-MeC_6H_4	**5f**	15	79	225-227
7	4-BrC_6H_4	**5g**	10	83	265-267
8	4-$NO_2C_6H_4$	**5h**	15	86	226-229
9	2,4-$Cl_2C_6H_3$	**5i**	10	89	219-222
10	3-BrC_6H_4	**5j**	10	84	260-264
11	Ph	**6a**	20	76	187-189
12	4-ClC_6H_4	**6b**	20	82	165-168
13	4-FC_6H_4	**6c**	30	89	103-105
14	3-BrC_6H_4	**6d**	35	78	176-178

[a]All the products were characterized by their M.ps (°C), and ^{1}H NMR and IR spectral analysis and compared with the literature data [21-26].
[b]Isolated yields.



Scheme 2. The proposed mechanism for synthesis of triazolo[1,2-a]indazole-1,3,8-trione and 2H-indazolo[2,1-b]phthalazine-trione derivatives.

spectrophotometer from KBr pellets. ^{1}H NMR spectra were measured for samples in $CDCl_3$ and DMSO-d6 using a BRUKER DRX-300 AVANCE instrument at 300.13 and 75.47 MHz respectively, using Me_4Si as internal standard. Melting points were measured on a SMPI apparatus. The complex tetrakis(acetonitrile)copper(I)hexafluorophosphate was synthesized according to the literature [27].

General Procedure for the Synthesis of Compounds 5 and 6

Aromatic aldehyde **1** (1.0 mmol), dimedone **2** (1.0 mmol), phthalhydrazide **3** (1.0 mmol), or 4-phenylurazole **4** (1.0 mmol) and $[Cu(CH_3CN)_4]PF_6$ (15 mol %) are placed in a mortar. The reaction mixture was then heated at 100 °C for an appropriate time (Table **1**) until the completion of the reaction was achieved as monitored by TLC. Then, the reaction mixture was cooled, washed with acetone (15 mL) and evaporated under vacuum to give the product, which was crystallized from ethyl acetate/n-hexane (1:3) to afford pure **5** or **6**.

3,4-Dihydro-3,3-dimethyl-13-(4-chlorophenyl)-2*H*-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**5b**): White powder (90%); mp 261-263 ^oC. IR (KBr) (vmax, cm^{-1}): 2959, 1659, 1625. ^1H NMR (300 MHz, $CDCl_3$): δ, ppm; 1.21 (6H, s, 2Me), 2.34 (2H, s, CH_2CO), 3.27 and 3.38 (2H, AB system, 2JHH = 19.1 Hz, CH_2), 6.42 (1H, s, CH), 7.20-8.36 (8H, m, H-Ar).

6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-fluorophenyl)-[1,2,4]-triazolo[1,2-a]indazole-1,3,8(2H,5H,9H)- trione (**6c**): White powder (89%); mp 103–105 ^oC. IR (KBr) (vmax, cm^{-1}): 2958, 1785, 1723, 1662. ^1H NMR (300 MHz, $CDCl_3$): δ, ppm; 1.21 (3H, s, Me), 1.22 (3H, s, Me), 2.35 (2H, s, CH_2CO), 2.92-3.10 (2H, AB system, 2JHH = 19.5 Hz, CH_2), 6.19 (1H, s, CH), 7.43–7.57 (9H, m, H–Ar).

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

CONFLICT OF INTEREST

Declared none.

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