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One-pot synthesis of aliphatic and aromatic 2*H*-indazolo[2,1-*b*]phthalazine-triones catalyzed by *N*-halosulfonamides under solvent-free conditions

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ABSTRACT

N, *N*, *N*′, *N*′-Tetrabromobenzene-1,3-disulfonamide and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) were used as efficient catalysts for the one-pot synthesis of aliphatic and aromatic 2*H*-indazolo[2,1-*b*]phthalazine-triones in excellent yields from aldehydes, phthalhydrazide, and dimedone at 80–100 °C under solvent-free conditions.

1. Introduction

The development of simple synthetic routes for complex organic molecules from readily available reagents is an important task in organic synthesis.[1] Multi-component reactions (MCRs) are significant tools for the rapid and efficient synthesis of a wide variety of organic molecules.[2] These reactions have been investigated extensively in organic and diversely oriented synthesis; primarily due to their ability to generate complex molecular functionality from simple starting materials via one-pot reaction.

Organic reactions under solvent-free conditions have attracted much interest from chemists particularly from the viewpoint of green chemistry. Green chemistry approaches are significant due to the reduction in byproducts, a reduction in produced waste, and reduction of energy cost. The possibility of performing multicomponent reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as ecological point of view.[3]

The synthesis of new heterocyclic compounds has always been a subject of great interest due to their wide applicability. Heterocyclic compounds occur very widely in nature and are essential to life. Amongst a large variety of heterocyclic compounds, heterocycles containing phthalazine moiety are of interest because they show some pharmacological and biological activities.[4–6] Phthalazine derivatives were reported to possess anticonvulsant,[7] cardiotonic,[8] and vasorelaxant activities.[9] Thus, the synthesis of phthalazine is an important and useful task in organic chemistry. In recent years, *p*-TSA,[10] H_2SO_4 in water–ethanol or ionic liquid,[11] and silica supported polyphosphoric acid,[12] have been utilized for this synthesis.

2. Results and discussion

In a continuation of our interest in the application of *N*, *N*, *N*′, *N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) [PBBS],[13] in organic synthesis,[13–21] we wish to report here a facile and improved protocol for preparation of aliphatic and aromatic 2*H*-indazolo[2,1-*b*]phthalazine-triones from phthalhydrazide, dimedone, and various aliphatic and aromatic aldehydes in the presence of TBBDA and PBBS as catalysts under solvent-free conditions (Scheme 1).

The advantages of TBBDA and PBBS are as follows:

1. The preparation of TBBDA and PBBS are easy.
2. TBBDA and PBBS are stable under atmospheric conditions for two months.

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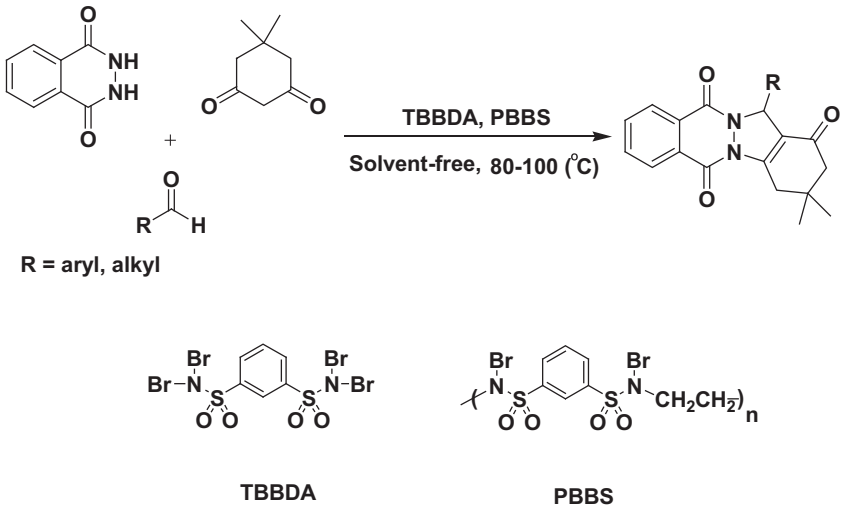

Scheme 1. Three-component synthesis of indazolo[2,1-*b*]phthalazine-triones derivatives.

3. After completion of the reaction, the catalysts are recovered and can be reused several times without decreasing the yield.

Initially, we decided to explore the role of our catalyst in ethanol and ethanol–water as solvent system for the synthesis of 3,3-dimethyl-13-phenyl-3,4-dihydro-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11(2*H*,13*H*)-trione (Table 2, entry 1) used as a model compound. In the absence of catalyst, no phthalazine was observed, even after prolonged reaction time. Since, the synthesis of phthalazine failed in the absence of catalyst, the effect of catalyst was also investigated in various conditions, and the results are presented in Table 1.

With respect to the solvent system, the best results were achieved using ethanol (Table 1, entry 2). In recent years, the synthesis of compounds under solvent-free is an important task in heterocyclic synthesis. Therefore, we decided to test this solvent-free reaction with various ratios of catalysts. We found that the reaction was rapid and gave excellent yields of the products when using *N*, *N*, *N*′, *N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] (10 min, 89%, entry 7).

Table 1
Reaction times and yields in various conditions

Entry	Solvent	Amount of catalyst[TBBDA (g)]	Temperature (°C)	Time (min)	Yield (%)
1	Ethanol	0.05 g	87	120	61%
2	Ethanol	0.1 g	87	90	70%
3	Ethanol	0.1 g	rt	90	—
4	Ethanol–water	0.05 g	100	120	60%
5	Ethanol–water	0.07 g	100	120	65%
6	Solvent-free	0.02 g	100	30	80%
7	Solvent-free	0.05 g	100	10	89%
8	Solvent-free	0.07 g	100	10	89%

These results encouraged us to investigate the scope and generality of this new protocol for various aliphatic and aromatic aldehydes under optimized conditions. As shown in Table 2, a series of aliphatic and aromatic aldehydes containing either electron-withdrawing or electron-donating substituents successfully react with phthalhydrazide and dimedone afforded good to high yields of products with high purity, at 80–100 °C under solvent-free conditions. It is noteworthy that there are no reports of the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones from aliphatic aldehydes.[10–12]

The nature and electronic properties of the aldehyde substrates affect the conversion rate and yield. Aromatic aldehydes (Table 2, entries 1–12) react faster and in higher yield than the aliphatic aldehydes (Table 2, entries 13–20).

It is likely that these reagents release Br^+ in situ, which can act as an electrophilic species.[13–21] Therefore, the mechanism shown in Scheme 2 can be suggested for the conversion of the phthalhydrazide, dimedone, and various aliphatic and aromatic aldehydes to 2*H*-indazolo[2,1-*b*]phthalazine-triones.[10]

3. Conclusion

In summary, we have developed a new facile protocol for the synthesis of new aliphatic and aromatic indazolo[2,1-*b*]phthalazine-triones derivatives from the reaction of aldehydes, phthalhydrazide and dimedone compounds using TBBDA and PBBS under solvent-free conditions.

4. Experimental

4.1. General

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purification unless otherwise stated. Nuclear magnetic resonance ^1H and ^{13}C NMR spectra (Sharif University and Urmia University) were recorded on Bruker Avance 300 and 500 MHz FT NMR spectrometers. Infrared (IR) spectroscopy was conducted on a Perkin Elmer GX FT-IR spectrometer. Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer. Elemental analyses (C, H, N) were performed with a Heraeus CHN-*O*-Rapid analyzer (University of Tarbiatmoallem, Tehran).

4.2. Typical procedure for the preparation of 3,4-dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[2, 1-*b*]phthalazine-1,6,11 (13*H*)-trione (Table 2, entry 1)

A mixture of dimedone (0.28 g, 2 mmol), phthalhydrazide (0.32 g, 2 mmol), benzaldehyde (0.24 g, 2.2 mmol), and TBBDA (0.05 g) or PBBS (0.1 g) was heated at 100 °C for 10 min. After