Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 78 (4) 469–476 (2013)
JSCS–4430
UDC 546.185–323+547.269.3+547.387'592+544.478
Original scientific paper

Phospho sulfonic acid: a novel and efficient solid acid catalyst for the one-pot preparation of indazolo[1,2-*b*]-phthalazinetriones

ALI REZA KIASAT*, ARASH MOURADZADEGUN and SEYYED JAFAR SAGHANEZHAD

Chemistry Department, College of Science, Shahid Chamran University, Ahvaz 61357-4-3169, Iran

(Received 8 May, revised 27 August 2012)

Abstract: An efficient one-pot condensation of aldehyde, dimedone and phthalhydrazide has been achieved in the presence of a catalytic amount of phospho sulfonic acid as a novel environmentally benign heterogeneous solid acid under solvent-free conditions. Diverse indazolo[1,2-*b*]phthalazinetrione derivatives were prepared in good to excellent yields in short times. The economical factors (time, cost, waste, *etc*.) for this three-component reaction hold promise for the future of organic synthesis.

Keywords: indazolo[1,2-*b*]phthalazinetrione; multicomponent reaction; phthalhydrazide; dimedone; solvent-free; phospho sulfonic acid.

INTRODUCTION

Multicomponent reactions (MCRs) are defined as one-pot processes in which three or more substrates combine either simultaneously (so-called tandem or domino reactions), or through a sequential addition procedure that does not require any change of solvent. MCRs are gaining more and more importance especially in the total synthesis of natural products and medicinal heterocyclic compounds because of their simplicity, high yield of the products and short reaction times.[1,2]

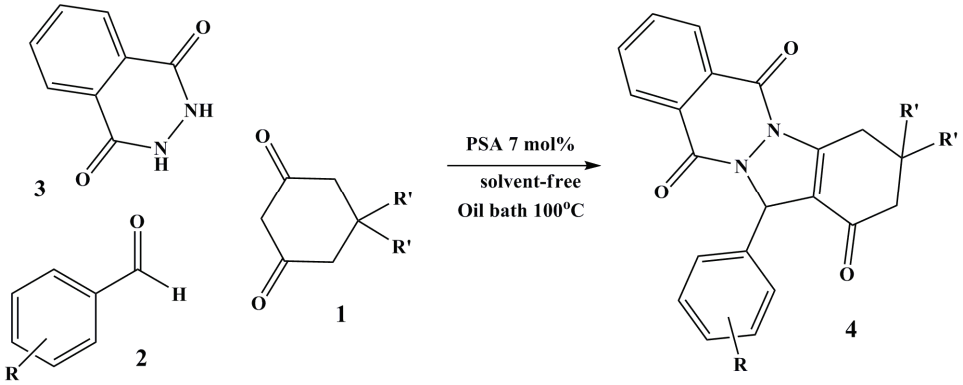
Solvent-free organic reactions have attracted much interest particularly from the viewpoint of green chemistry. Solid-state reactions (or solvent-free reactions) have many advantages, such as reduced pollution, low costs and simplicity in the process and handling.[3] The possibility of performing multicomponent reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from economic and ecological points of view.[4]

* Corresponding author. E-mail: akiasat@scu.ac.ir
doi: 10.2298/JSC120508088K

The synthesis of new heterocyclic compounds has always been a subject of great interest due to their wide applicability. Among a large variety of heterocyclic compounds, heterocycles containing phthalazine moiety are of interest because they show several pharmacological and biological activities.[5–7] Phthalazine derivatives, which have two bridgehead nitrogen atoms in a fused ring system, possess cytotoxic,[8] antimicrobial,[9] anticonvulsant,[10] antifungal,[11] anticancer[12] and anti-inflammatory[13] activities. Moreover, these compounds exhibited good promise as new luminescent materials or fluorescence probes.[14]

The first synthesis of indazolo[1,2-*b*]phthalazinetriones was reported by Bazgir *et al*. using *p*-toluenesulfonic acid (*p*-TSA) as a catalyst[15]. In recent years, silica sulfuric acid,[16] H_2SO_4 in water–ethanol or an ionic liquid,[17] silica-supported polyphosphoric acid,[18] $Mg(HSO_4)_2$[19] heteropoly acids,[20] *N*-halosulfonamides,[21] sulfonated poly(ethylene glycol),[22] wet cyanuric chloride,[23] molecular iodine[24] and nanosilica sulfuric acid,[25] have been utilized for the three-component condensation of 1,3-dicarbonyls, aromatic or aliphatic aldehydes and phthalhydrazide/urazole. Moreover, there are a few reports about the four-component condensation of phthalic anhydride, hydrazinium hydroxide, aromatic aldehydes and dimedone using $Ce(SO_4)_2 \cdot 4H_2O$[26] or 1-butyl-3-methylimidazolium bromide ([Bmim]Br).[27]

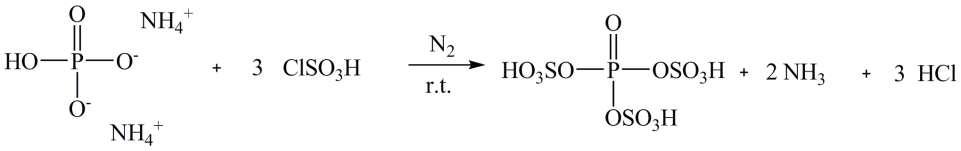
The aim of this presented protocol is to highlight the synergistic effects of the combined use of MCRs and reactions under solvent-free conditions with a heterogeneous catalyst for the development of a new eco-compatible strategy for the synthesis of heterocyclics. Therefore, a straightforward convergent one-pot synthesis of indazolo[1,2-*b*]phthalazinetrione derivatives using phospho sulfonic acid as an efficient solid acid catalyst under solvent-free conditions through the domino Knoevenagel condensation/Michael addition/intramolecular cyclodehydration sequence was examined (Scheme 1).



Scheme 1. Three-component reaction of dimedone, phthalhydrazide and aromatic aldehydes.

RESULTS AND DISCUSSION

Phospho sulfonic acid, PSA, was easily prepared by the simple mixing of diammonium hydrogen phosphate and chlorosulfonic acid in CH_2Cl_2 at room temperature (Scheme 2). This reaction is easy and clean because the by-products of the reaction are HCl and NH_3 gases, which are immediately evolved from the reaction vessel.



Scheme 2. Preparation of the catalyst.

To evaluate the catalytic activity of PSA in the preparation of indazolo[1,2--*b*]phthalazine-1,6,11-trione derivatives, a model three-component coupling reaction of phthalhydrazide (1 mmol), dimedone (1 mmol) and benzaldehyde (1.1 mmol) under solvent-free conditions at 100 °C in the absence and presence of PSA were examined. It was found that in the absence of solid acid catalyst, only trace amount of the desired product was observed on TLC plate even after 1 h of heating (Table I). When the reaction was performed in the presence of PSA, it proceeded rapidly to give the desired product.

TABLE I. Optimization of the conditions for the three-component condensation reaction of phthalhydrazide (1 mmol), dimedone (1 mmol) and benzaldehyde (1.1 mmol) under thermal (100 °C) solvent-free conditions

Entry	Catalyst amount, mol %	Temperature, °C	Time, min	Yield, %
1	–	100	60	–
2	3.5	100	45	85
3	7	100	10	91
4	9.5	100	8	90
5	7	25	60	–
6	7	60	60	40

In order to evaluate the appropriate catalyst loading, a model reaction was performed using 3.5 to 9.5 mol % catalyst at different temperatures without solvent (Table I). It was found that 7 mol % of the catalyst resulted in the maximum yield in the minimum time. A higher percentage of loading of the catalyst (9.5 mol %) neither increased the yield nor shortened the conversion time. Next, the effect of temperature was evaluated for the model reaction. It was observed that the reaction did not proceed at room temperature. Elevating the reaction temperature proved helpful, and the yield of desired product increased considerably. It was gratifying to find that the reaction proceeded smoothly and almost

complete conversion to the product was observed at 100 °C, affording 2,3,4,13--tetrahydro-3,3-dimethyl-13-phenyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione in 91 % yield within a short time.

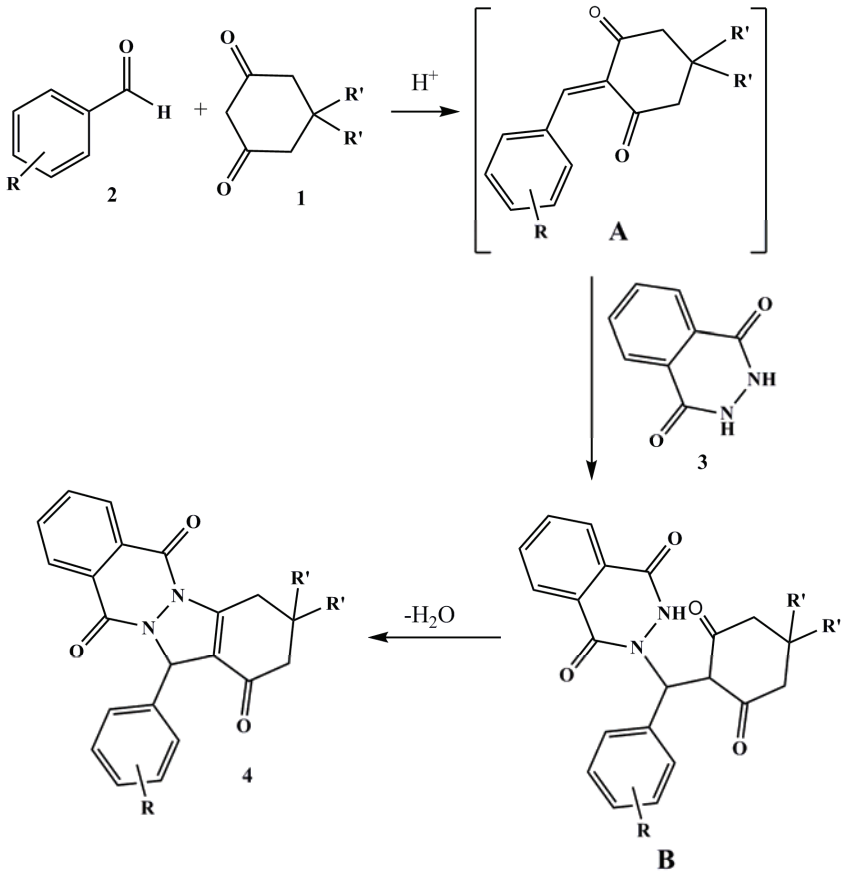
Subsequently, with optimal conditions at hand, *i.e.*, 1.1:1:1 molar ratios of aldehyde, dimedone and phthalhydrazide and 7 mol % of PSA at 100 °C under solvent-free conditions, the generality and synthetic scope of this coupling protocol were demonstrated by synthesizing a series of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones (Table II). Gratifyingly, a wide range of aromatic aldehydes was well tolerated under the optimized reaction conditions. The time taken for complete conversion (monitored by TLC) and the isolated yields are presented in Table II. All new compounds were characterized by their satisfactory spectral (IR, ^{1}H-NMR and ^{13}C-NMR) studies, and the known compounds by comparison of their physical and spectral data with those reported.

TABLE II. The one-pot preparation of 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione derivatives promoted by PSA under solvent-free conditions at 100 °C

Product	R	R′	Time, min	Yield, %	Melting point, °C	
					Found	Lit.
4a	H	CH_3	10	91	208–210	207–209[15]
4b	4-NO_2	CH_3	4	89	220–222	223–225[15]
4c	3-NO_2	CH_3	5	98	269–272	270–272[15]
4d	2-Cl	CH_3	11	88	265–267	264–266[15]
4e	4-CH_3	CH_3	10	94	227–228	227–229[15]
4f	4-Cl	CH_3	5	92	262–264	262–264[15]
4g	4-OCH_3	CH_3	10	95	218–220	218–220[17]
4h	2,4-Cl_2	CH_3	15	86	220	219–221[18]
4i	3-CF_3	CH_3	8	98	214	213–215[20]
4j	3-CH_3	CH_3	10	91	232	232–233[20]
4k	4-CF_3	H	15	75	265	–

As shown in Table II, aromatic aldehydes having electron-releasing, as well as electron-withdrawing, groups were uniformly transformed into the corresponding indazolo[1,2-*b*]phthalazinetriones in high to excellent yields within 4–15 min. Substituents on the aromatic ring had no obvious effect on yield or reaction time under the above optimal conditions.

A plausible mechanistic rationale portraying a sequence of events for this coupling reaction is postulated in Scheme 3. The first step is believed to be the acid-catalyzed Knoevenagel condensation between the aldehyde and dimedone to generate adduct A, which acts as a Michael acceptor. The phthalhydrazide attacks adduct A in a Michael-type fashion to produce an open chain intermediate B. Intermediate B undergoes intramolecular cyclization by the reaction of nucleophilic amino function to carbonyl group followed by dehydration to form indazolo[1,2-*b*]phthalazinetriones.



Scheme 3. A plausible reaction mechanism.

The reusability of the catalyst in the reaction of dimedone, phthalhydrazide, and benzaldehyde, under solvent-free conditions at 100 °C was evaluated. In this procedure, after completion of each reaction, hot ethanol was added and the catalyst was filtered. The recovered catalyst was washed with ethanol, dried and reused five times. A mild depression in the catalytic activity of the catalyst was observed after the 5th time of reuse (Table III).

To compare the advantages of the employment of PSA over other reported catalysts, the model reaction of dimedone, phthalhydrazide and benzaldehyde was considered as a representative example (Table IV). While in most of these cases, comparative yields of the desired product were obtained as when the PSA--catalyzed procedure was followed, the reported procedures required high catalyst loading (entries 1, 2 and 4), or long reaction times (entries 3 and 5). These results clearly demonstrate that PSA is an equally or more efficient catalyst for this three-component reaction.

TABLE III. The reusability of the catalyst in five cycles for the reaction of dimedone, phthalhydrazide and benzaldehyde, under solvent-free conditions at 100 °C

Run	Time, min	Yield, %
1	10	91
2	10	90
3	11	88
4	12	85
5	13	82

TABLE IV. Comparison of PSA with reported catalysts in the reaction of dimedone, phthalhydrazide and benzaldehyde, under solvent-free conditions

Entry	Catalyst/temperature, °C	Catalyst loading mol %	Time, min	Yield, %	Ref.
1	*p*-Toluenesulfonic acid/80	30	10	86	15
2	Silica-supported PPA/80	0.1 g	7	91	18
3	Cyanuric chloride/100	3	15	96	23
4	$Mg(HSO_4)_2$/100	11.5	10	85	19
5	$H_4SiW_{12}O_{40}$/100	1	16	92	20
6	PSA/100	7	10	91	This work

EXPERIMENTAL

All commercially available chemicals were purchased from Fluka or Merck and used without further purification. The IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker Advanced DPX 400 MHz spectrometer using TMS as an internal standard. The obtained spectral data are given in the Supplementary material to this paper. Reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates.

Preparation of phospho sulfonic acid

A 50 mL suction flask was equipped with a constant-pressure dropping funnel. The gas outlet was connected to a vacuum system through an alkali solution trap. Diammonium hydrogen phosphate (2 g, 15 mmol) was charged into the flask and chlorosulfonic acid (5.24 g, *ca.* 3 mL, 45 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 30 min at room temperature. After completion of the addition, the mixture was shaken for 2 h, while the residual HCl was eliminated by suction. Then the mixture was washed with excess dried CH_2Cl_2. Finally, a solid white powder (4.2 g) was obtained. The FT-IR spectrum of the catalyst (KBr disk), showed O=S=O asymmetric and symmetric stretching peaks at 1124 and 1075 cm^{-1}, respectively, and the S–O stretching peak at 678 cm^{-1}, which strictly confirmed the sulfonic group linkage.

*Typical procedure for the preparation of indazolo[1,2-*b*]phthalazinetriones*

A mixture of dimedone (0.14 g, 1.0 mmol), phthalhydrazide (0.16 g, 1.0 mmol), an aromatic aldehyde (1.1 mmol) and PSA (0.05 g) was heated at 100 °C for 10 min. Completion of the reaction was indicated by TLC [TLC acetone/*n*-hexane (3:10)]. After completion of the reaction, the insoluble crude product was dissolved in hot ethanol and phospho sulfuric acid was filtered off. The crude product was purified by recrystallization from ethanol to afford the pure product.

CONCLUSIONS

In summary, a simple and facile protocol has been described for the synthesis of indazolo[1,2-*b*]phthalazinetrione derivatives from a one-pot, three-component condensation reaction of aromatic aldehydes, phthalhydrazide and dimedone under solvent-free conditions using phospho sulfonic acid as a novel environmentally safe heterogeneous solid acid catalyst. The method offers several advantages, including high yields, application of an inexpensive catalyst, short reaction times, easy workup and performing a multicomponent reaction under solvent-free conditions that is considered relatively environmentally benign.

SUPPLEMENTARY MATERIAL

Spectral data for obtained compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgement. We gratefully acknowledge the support of this work by Shahid Chamran University Research Council, Iran.

ИЗВОД

ФОСФО-СУЛФОНСКА КИСЕЛИНА: НОВ И ЕФИКАСАН КИСЕЛИ КАТАЛИЗАТОР У ЧВРСТОЈ ФАЗИ ЗА СИНТЕЗУ ИНДАЗОЛО[1,2-*b*]ФТАЛАЗИН-ТРИОНА У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ

ALI REZA KIASAT, ARASH MOURADZADEGUN и SEYYED JAFAR SAGHANEZHAD

Chemistry Department, College of Science, Shahid Chamran University, Ahvaz 61357-4-3169, Iran

Постигнута је ефикасна кондензација, у једном реакционом кораку, алдехида, димедона и фталхидразида, у присуству каталитичких количина фосфо-сулфонске киселине као новог, еколошки прихватљивог хетерогеног катализатора у одсуству органских растварача. Добијена је серија деривата индазоло[1,2-*b*]фталазин-триона у добром до одличном приносу за кратко реакционо време. Економски показатељи (време, цена и губици) за ову трокомпонентну реакцију пружају основ за даљи развој поступка.

(Примљено 8. маја, ревидирано 27. августа 2012)

REFERENCES

1. B. B. Toure, D. G. Hall, in *Multicomponent Reactions*, J. Zhu, H. Bienayme, Eds., Wiley-VCH, Weinheim, Germany, 2005, p. 342
2. N. Shajari, A. R. Kazemizadeh, A. Ramazani, *J. Serb. Chem. Soc.* **77** (2012) 1175
3. K. Tanaka, F. Toda, *Chem. Rev.* **100** (2000) 1025
4. A. Kumar, R. A. Maurya, *Tetrahedron* **63** (2007) 1946
5. F. Al-Assar, K. N. Zelenin, E. E. Lesiovskaya, I. P. Bezhan, B. A. Chakchir, *Pharm. Chem. J.* **36** (2002) 598
6. R. P. Jain, J. C. Vederas, *Bioorg. Med. Chem. Lett.* **14** (2004) 3655
7. R. W. Carling, K. W. Moore, L. J. Street, D. Wild, C. Isted, P. D. Leeson, S. Thomas, D. O'Conner, R. M. McKernan, K. Quirk, S. M. Cook, J. R. Atack, K. A. Wafford, S. A. Thompson, G. R. Dawson, P. Ferris, J. L. Castro, *J. Med. Chem.* **47** (2004) 1807
8. J. S. Kim, H. K. Rhee, H. J. Park, S. K. Lee, C. O. Lee, H. Y. Park Choo, *Bioorg. Med. Chem.* **16** (2008) 4545

9. S. S. El-Sakka, A. H. Soliman, A. M. Imam, *Afinidad* **66** (2009) 167
10. L. Zhang, L. P. Guan, X. Y. Sun, C. X. Wei, K. Y. Chai, Z. S. Quan, *Chem. Biol. Drug Design* **73** (2009) 313
11. C. K. Ryu, R. E. Park, M. Y. Ma, J. H. Nho, *Bioorg. Med. Chem. Lett.* **17** (2007) 2577
12. J. Li, Y. F. Zhao, X. Y. Yuan, J. X. Xu, P. Gong, *Molecules* **11** (2006) 574
13. J. Sinkkonen, V. Ovcharenko, K. N. Zelenin, I. P. Bezhan, B. A. Chakchir, F. Al-Assar, K. Pihlaja, *Eur. J. Org. Chem.* (2002) 2046
14. H. Wu, X. M. Chen, Y. Wan, H. Q. Xin, H. H. Xu, R. Ma, C. H. Yue, L. L. Pang, *Lett. Org. Chem.* **6** (2009) 219
15. M. Sayyafi, M. Seyyedhamzeh, H. R. Khavasi, A. Bazgir, *Tetrahedron* **64** (2008) 2375
16. H. R. Shaterian, M. Ghashang, M. Feyzi, *Appl. Catal., A* **345** (2008) 128
17. J. M. Khurana, D. Magoo, *Tetrahedron Lett.* **50** (2009) 7300
18. H. R. Shaterian, A. Hosseinian, M. Ghashang, *ARKIVOC* (2009) 59
19. H. R. Shaterian, F. Khorami, A. Amirzadeh, R. Doostmohammadi, M. Ghashang, *J. Iran. Chem. Res.* **2** (2009) 57
20. H. J. Wang, X. N. Zhang, Z. H. Zhang, *Monatsh. Chem.* **141** (2010) 425
21. R. Ghorbani-Vaghei, R. Karimi-Nami, Z. Toghraei-Semiromi, M. Amiri, M. Ghavidel, *Tetrahedron* **67** (2011) 1930
22. A. Hasaninejad, A. Zare, M. Shekouhy, *Tetrahedron* **67** (2011) 390
23. X. Wang, W. Ma, L. Wu, F. L. Yan, *J. Chin. Chem. Soc.* **57** (2010) 1341
24. X. Wang, G. Lu, W. Ma, L. Wu, *E-J. Chem.* **8** (2011) 1000
25. H. Hamidian, S. Fozooni, A. Hassankhani, S. Z. Mohammadi, *Molecules* **16** (2011) 9041
26. E. Mosaddegh, A. Hassankhani, *Tetrahedron Lett.* **52** (2011) 488
27. M. Shekouhy, A. Hasaninejad, *Ultrason. Sonochem.* **19** (2012) 307.