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Synthesis of tetrasubstituted 1*H*-indazolo[1,2-*b*] phthalazinedione derivatives bearing three-dimensional turbine-type structures *via* domino reaction of phthalhydrazide and vinylketones†

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A domino reaction of phthalhydrazide and vinylketone in the presence of phosphotungstic acid was successfully established, and 3D turbine-type tetrasubstituted 1*H*-indazolo[1,2-*b*]phthalazinedione derivatives were conveniently obtained with moderate to excellent yields (up to 95%). The highly efficient catalytic system exhibited broad substrate scopes under mild conditions. A 78% yield of the desired product was obtained when the reaction was conducted on a multi-gram scale.

Molecules bearing special structures are versatile and fascinating building blocks that self-assemble.[1] Particularly, those bearing special one-dimensional (1D), two-dimensional (2D) and three-dimensional (3D) structures have unique and tunable optical or electronic properties and are, therefore, widely used in supramolecular chemistry to create advanced functional materials.[2] To the best of our knowledge, numerous molecules with 1D and 2D structures have been designed and developed in the past decades;[3–6] however, except for porphyrin derivatives and their modifications, molecules with 3D structure have been rarely used,[7] despite their better assembly capability and properties than those with 1D and 2D structures. Thus, designing and synthesizing novel molecules with 3D structure are highly significant for studying supramolecular chemistry and soft material science.

Phthalazine-fused cyclic skeletons are received considerable attention due to their pharmacological properties and applications in luminescence materials or fluorescence probes.[8] Among these compounds, 1*H*-indazolo[1,2-*b*]phthalazinediones (IPDs) contain fused hydrazine-based pyrazole heterocycles and nearly planar structures that are widely distributed in self-assembly, molecular recognition, sensors, and optical/electronic materials.[9] Their medicinal relevance and structural characteristic have led to the development of efficient synthetic protocols for the constructing such skeletons.[10,11] The established strategies mainly involve cyclo-condensation of ketones[10] or malononitrile,[11] as well as aldehydes and phthalhydrazide, promoted by Brønsted acid (SiO_2/SO_3H,[10a] H_2SO_4,[10b] heteropolyacids,[10c–e] *p*-toluenesulfunic acid,[10f] (*S*)-CSA[10g]), or Lewis acid ($Fe_2(SO_4)_3 \cdot xH_2O$,[10h] $Ce(SO_4)_2 \cdot 4H_2O$,[10f]). However, these approaches mainly focus on the construction of disubstituted IPDs. Preparation methods for tetrasubstituted IPDs are limited. Likewise, tetrasubstituted IPDs have an interesting 3D turbine-type structure that can be used in supramolecular chemistry and functional materials. To the best of our knowledge, these novel 3D structural molecules have been rarely studied.

Though the developed cyclo condensation reaction has emerged as a powerful tool to synthesize diverse disubstituted IPDs,[10,11] it does not work in the application for synthesis of tetrasubstituted IPDs. Therefore, it is still highly challenging and desirable to develop efficient strategies to access novel tetrasubstituted IPDs with 3D structures.

Solid acids have attracted much attention from chemists because of their easy recovery and recycling in organic synthesis applications. Among these acids, heteropolyacids are environment-friendly and have high stability towards humidity, easy recovery, and recyclability.[12] Based on this background and our continuing interest in the development of useful synthetic methodologies,[13] we envisioned that the aza-Michael addition reaction of phthalhydrazide and vinylketone could be achieved in the presence of an appropriate Brønsted acid, and subsequently Michael addition reaction with another vinylketones occurred. Then, intramolecular Michael addition and condensation reaction occurred to give the tetrasubstituted IPDs. This transformation involves two intermolecular Michael additions, namely, an intramolecular Michael addition and a condensation reaction. Herein, we wish to report our preliminary results on the first efficient synthesis of tetrasubstituted IPDs with phthalhydrazide and two vinylketones as reactants in the presence of phosphotungstic acid under mild conditions.

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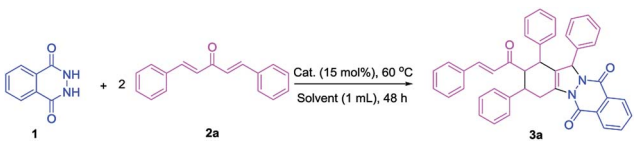
† Electronic supplementary information (ESI) available: X-ray crystallographic data for compound **3g**. Copies of ^{1}H NMR and ^{13}C NMR of products. CCDC 1554488. For ESI and crystallographic data in CIF or other electronic format see DOI:10.1039/c7ra06856e

Phthalhydrazide (**1a**) and **2a** were selected as model substrates to test the feasibility of our hypothesis. The reaction proceeded smoothly in the presence of phosphotungstic acid and successfully produced the desired product **3a** (49% yield, Table 1, entry 1). The reaction of phthalhydrazide and vinylketone was performed in CH_3CN without a catalyst at 60 °C for the comparative group. As expected, the reaction did not occur even after 48 h (Table 1, entry 2). Moreover, the use of different Lewis acids as catalysts was investigated to develop an efficient catalytic system. The results were dissatisfactory, and only $AlCl_3$ produced the desired product **3a** with a 13% yield (Table 1, entry 3). Furthermore, several Brønsted acids were screened. When the reaction was performed using $PhCO_2H$, CF_3CO_2H, CF_3SO_3H, or HCl as the catalysts, only CF_3SO_3H produced the desired product with a moderate yield (49%, Table 1, entry 8). Among the screened catalysts, both phosphotungstic and trifluoromethanesulfonic acid produced the desired products in almost similar yields and were, therefore, selected as the catalysts for further optimization (entries 1 and 8).

The solvents were examined using phosphotungstic or trifluoromethanesulfonic acid as the catalyst at 60 °C to further optimize the reaction conditions and the results described in Table 1 (entries 10–12). As it turned out, the results were significantly dependent on the reaction media. When phosphotungstic acid was used as the catalyst, PhCN produced the best yield among the screened solvents (92%, Table 1, entry 13).

The effects of reaction temperature on PhCN were examined using phosphotungstic acid as the catalyst. When the temperature was lowered to 40 °C, the yield was decreased significantly (60% yield, Table 1, entry 17). When the catalyst loading was reduced to 10 mol%, the yield was decreased as well (87%, Table 1, entries 18 *vs.* 13). Comparatively, when the reaction was carried out in the absence of the catalyst, no desired product was obtained (Table 1, entry 20). Thus, the optimized reaction conditions were found to be the reaction of 1.0 equiv. phthalhydrazide with 2.0 equiv. **2a** in the presence of 15 mol% of phosphotungstic acid in cyanobenzene at 60 °C (Table 1, entry 13).

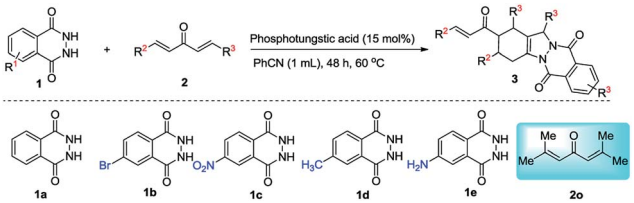
Table 1 Screening of catalysts and optimized the conditions[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	Phosphotungstic acid	CH_3CN	49
2	—	CH_3CN	NR
3	$FeCl_3$	CH_3CN	NR
4	$CuCl_2$	CH_3CN	Trace
5	$AlCl_3$	CH_3CN	13
6	$PhCO_2H$	CH_3CN	NR
7	CF_3CO_2H	CH_3CN	Trace
8	CF_3SO_3H	CH_3CN	49
9	HCl	CH_3CN	Trace
10	Phosphotungstic acid	THF	64 (14)[c]
11	Phosphotungstic acid	Dioxane	10 (9)[c]
12	Phosphotungstic acid	DMC	36 (trace)[c]
13	Phosphotungstic acid	PhCN	92 (trace)[c]
14	Phosphotungstic acid	PhMe	24 (trace)[c]
15	Phosphotungstic acid	$CHCl_3$	11 (trace)[c]
16	Phosphotungstic acid	DMF	10 (22)[c]
17[d]	Phosphotungstic acid	PhCN	60
18[e]	Phosphotungstic acid	PhCN	87
19[f]	Phosphotungstic acid	PhCN	68
20[g]	Phosphotungstic acid	PhCN	NR

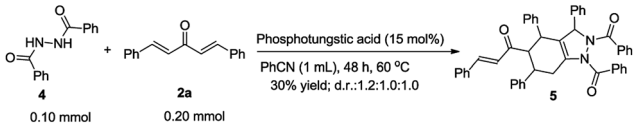
[a] Unless otherwise specified, all reaction carried out with phthalhydrazide (0.10 mmol, 1.0 equiv.), vinylketone (**2a**, 0.20 mmol, 2.0 equiv.), solvent (1 mL) and catalysts (15 mol%) at 60 °C. [b] Isolated yields. [c] The yields in parenthesis are the isolated yields using trifluoromethanesulfonic acid as the catalyst. [d] Carried out at 40 °C. [e] Carried out with 10 mol% phosphotungstic acid. [f] Carried out with phthalhydrazide (0.10 mmol, 1.0 equiv.), vinylketone (**2a**, 0.10 mmol, 1.0 equiv.), PhCN (1 mL) and catalyst (15 mol%) at 60 °C. [g] Carried out with phthalhydrazide (0.10 mmol, 1.0 equiv.), vinylketone (**2a**, 0.10 mmol, 1.0 equiv.) and PhCN (1 mL) at 60 °C.

Table 2 Scope of substrates[a]

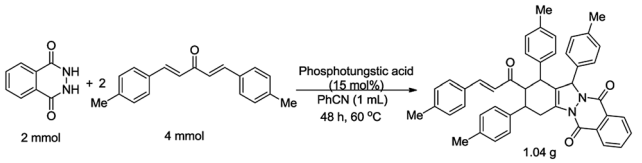


Entry	1	2	d.r.[b]	Yield[c] (%)
1	**1a**	**2a**: $R^2 = R^3$ = Ph	2.5 : 1.8 : 1.0	92 (**3a**)
2	**1a**	**2b**: $R^2 = R^3$ = 4-FPh	1.8 : 1.1 : 1.0	60 (**3b**)
3	**1a**	**2c**: $R^2 = R^3$ = 4-ClPh	3.2 : 2.4 : 1.0	84 (**3c**)
4	**1a**	**2d**: $R^2 = R^3$ = 4-BrPh	1.8 : 1.3 : 1.0	89 (**3d**)
5	**1a**	**2e**: $R^2 = R^3$ = 4-CF_3Ph	1.6 : 1.0	40 (**3e**)
6	**1a**	**2f**: $R^2 = R^3$ = 4-CH_3OPh	2.8 : 1.0	91 (**3f**)
7	**1a**	**2g**: $R^2 = R^3$ = 4-CH_3Ph	1.4 : 1.0	90 (**3g**)
8	**1a**	**2h**: $R^2 = R^3$ = 3-ClPh	1.8 : 1.0	62 (**3h**)
9	**1a**	**2i**: $R^2 = R^3$ = 3-CH_3OPh	>20 : 1	89 (**3i**)
10	**1a**	**2j**: $R^2 = R^3$ = 3-CH_3Ph	1.7 : 1.0	86 (**3j**)
11	**1a**	**2k**: $R^2 = R^3$ = 2-BrPh	n.d.	—[d] (**3k**)
12	**1a**	**2l**: $R^2 = R^3$ = 2-CH_3Ph	n.d.	—[d] (**3l**)
13	**1a**	**2m**: R^2 = R^3 = 1-naphthyl	—[e]	95 (**3m**)
14	**1a**	**2n**: R^2 = Ph, R^3 = 3-CH_3OPh	—[e]	85 (**3n**)
15	**1a**	**2o**	n.d.	Trace
16	**1b**	**2a**	n.d.	Trace
17	**1c**	**2a**	2.8 : 1.0 : 1.0	87 (**3q**)
18	**1d**	**2a**	4.4 : 4.4 : 1.0 : 1.0	63 (**3r**)
19	**1e**	**2a**	4.9 : 2.4 : 1.0	69 (**3s**)

[a] All reaction carried out with phthalhydrazide (0.10 mmol, 1.0 equiv.), vinylketone (**2**, 0.20 mmol, 2.0 equiv.), cyanobenzene (1 mL) and phosphotungstic acid (15 mol%) at 60 °C. [b] Diasteromeric ratio was determined by ^{1}H NMR analysis. [c] Isolated yield. [d] The reaction mixture became messy and no desired product was obtained. [e] The d.r. value was not determined because that the main characteristic peaks of the ^{1}H NMR spectra were not found.



Scheme 1 Domino reaction of *N,N′*-dibenzoylhydrazine and **2a**.

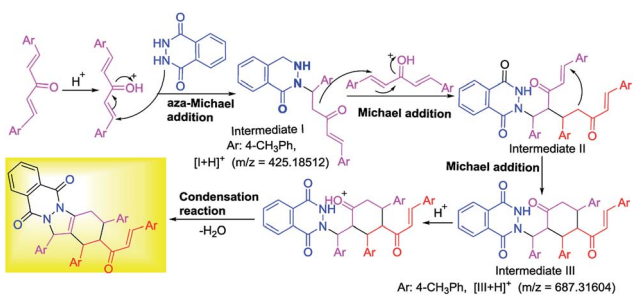


Scheme 2 Gram-scale preparation of **3g**.

To broaden the substrate scopes, the reaction generality was examined with the domino reaction of phthalhydrazide (**1**) with various vinylketones (**2**) under optimized conditions, and the results are listed in Table 2. Various electron-withdrawing groups (4-F, 4-Cl, 4-Br, 4-CF_3, Table 2, entries 2–5) and electron-donating groups (4-CH_3O, 4-CH_3, Table 2, entries 6 and 7) at the 4-position on the aromatic ring of **2** were completely tolerated in the transformation. And the electron-donating groups at the 4-position on the aromatic ring of **2** gave relatively higher yields than those with electron-withdrawing groups. Furthermore, the positions of the substituents on the aryl group of **2** were studied. Unfortunately, the vinylketones with electron-withdrawing or -donating substituents on the aromatic ring at the 2-position produced no desired products as the reaction mixture became merry (Table 2, entries 11 and 12). The position of the substituents on the aromatic ring of **2** was more important than the electronic property of the substituents. An excellent yield of 95% was obtained when 1-naphthyl was used to substitute the vinylketones (Table 2, entry 13).

Delightedly, when the domino reaction of phthalhydrazide and unsymmetric vinylketone **2n** was conducted under optimized reaction conditions, the desired product with a good yield was obtained (85%, Table 2, entry 14). When a multi-substituted **2o** was used, only trace of the desired product was obtained because of the steric hindrance (Table 2, entry 15).

This method is compatible with phthalhydrazide which has diverse electronic properties substituent in aryl ring (Table 2, entries 16–19). The electron-deficient 4-NO_2 substituted



Scheme 3 Proposed reaction mechanism.

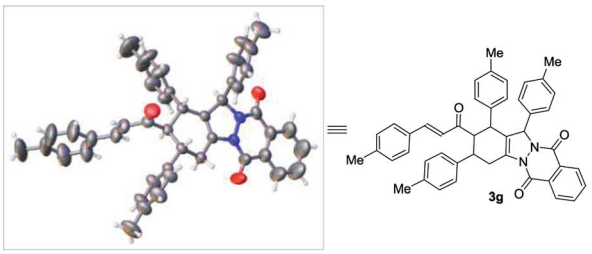


Fig. 1 X-ray crystal structure of **3g** with thermal ellipsoid contour at 30% probability level.

phthalhydrazide (**2b**) led to relatively high yield of the corresponding formation (87%, Table 2, entry 16). The reaction of electron-rich group substituted phthalhydrazides with **2a** afforded moderate yields (63–69%, Table 2, entries 18 and 19).

For the open-chain *N,N′*-dibenzoylhydrazine, the domino reaction still proceeded smoothly and resulted in a corresponding product with 30% yield (Scheme 1).

To demonstrate the synthetic potential of the transformation, a gram-scale experiment was conducted with 2.0 mmol **1a** and 4.0 mmol **2g**. This reaction proceeded smoothly and afforded the domino product **3g** with 78% yield (Scheme 2).

In order to clarify the structure of the product, we studied the X-ray crystallographic analysis of **3g** (Fig. 1).

Based on Brønsted acids catalysis, the experimental results and HRMS analysis, a possible mechanism was proposed for synthesis of tetrasubstituted IPDs as shown in Scheme 3. Initially, vinylketone was activated by phosphotungstic acid, and then trapped by phthalhydrazide **1a** to undergo aza-Michael addition reaction, leading to the formation of intermediate **I**. An intermolecular Michael addition reaction between intermediate **I** and another vinylketones affording intermediate **II**. And then intramolecular Michael addition reaction of intermediate **II** occurred giving intermediate **III**. Finally, the condensation reaction of intermediate **III** and dehydration occurred, which furnished the desired compound and released the catalyst. ESI-HRMS analysis and control experiments were conducted to support the proposed catalytic cycle. Firstly, the intermediates **I** and **III** were supported by ESI-HRMS. A characteristic signal at *m/z* 691.28589 was observed, which was consistent with $[\mathbf{3g} + Na]^+$, and $[\mathbf{I} + H]^+$ at 425.18512 as well as $[\mathbf{III} + H]^+$ at 687.31604 (Scheme 3 and see detail in ESI Fig. S1†).

Conclusions

In summary, we successfully developed a simple and efficient domino reaction for constructing 3D turbine-type tetrasubstituted IPDs. In the presence of phosphotungstic acid, the reaction between phthalhydrazide and vinylketone could proceed smoothly and produced a series of 3D turbine-type tetrasubstituted IPDs in excellent yields (up to 95%). This protocol provides a valuable access to novel tetrasubstituted IPDs with a 3D turbine-type structures, which would be applied in supramolecular chemistry, functional materials and medicinal chemistry. And the application of the tetrasubstituted IPDs in supramolecular chemistry is currently being studied in our laboratory.

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