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$PhI(OAc)_2$-Mediated Novel 1,3-Dipolar Cycloaddition of Methylenecyclopropanes (MCPs), Vinylidenecyclopropanes (VCPs), and Methylenecyclobutane (MCB) with Phthalhydrazide

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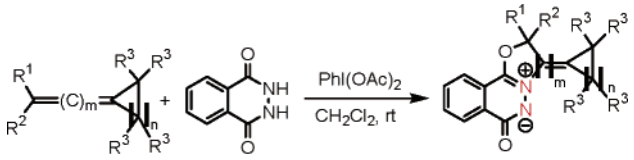
ABSTRACT



R^1, R^2 = Ar, H or Me, R^3 = H or Me, m = 0 or 1, n = 1 or 2

Iodobenzene diacetate-mediated reactions of methylenecyclopropanes 1, vinylidenecyclopropanes 2, and a methylenecyclobutane 3a with phthalhydrazide give the corresponding [3+2] cycloaddition products in good yields under mild conditions. In these reactions, phthalhydrazide was transformed to a 1,3-dipole intermediate in the presence of iodobenzene diacetate. A plausible reaction mechanism has been proposed.

The involvement in cycloaddition reactions is the most typical reactivity of methylenecyclopropanes (MCPs) **1**, which are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1,2] MCPs can be the substrates for Diels−Alder or 1,3-dipolar cycloadditions because they are strained alkenes.[3] Recently, a variety of ring-opening or ring-enlargement reactions of MCPs in the presence of transition metal or Lewis acid have been reported.[4] Brandi and co-workers have studied the 1,3-dipolar cycloaddition of MCPs with nitrones and nitrile oxides for a long time and much brilliant work has been published in the literature.[5] In addition, in recent years, Che[6] and Yudin[7] independently found that *N*-aminophthalimide could be used as a nitrene equivalent for the aziridination of olefins under the promotion of iodobenzene diacetate. Most recently, Yu and co-workers employed this protocol for amidation of MCPs and a methylenecyclobutane (MCB) to produce a series of ring-enlargement products.[8] Interestingly, we found that using phthalhydrazide as an alternative in a similar reaction, a novel 1,3-dipolar cycload-

(1) For synthesis of MCPs: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589.

(2) For recent reviews on MCPs, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89. (c) Binger, P.; Wedemann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113. (d) de Meijere, A.; Kozhushkov, S. I. *Eur. J. Org. Chem.* **2000**, 3809. (e) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (f) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (g) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867.

(3) See ref 2f and references cited therein, also see: (a) Molchanov, A. P.; Diev, V. V.; Magull, J.; Vidovic, D.; Kozhushkov, S. I.; de Meijere, A.; Kostikov, R. R. *Eur. J. Org. Chem.* **2005**, 593. (b) de Meijere, A.; Becker, H.; Stolle, A.; Kozhushkov, S. I.; Bes, M. T.; Salaün, J.; Noltemeyer, M. *Chem. Eur. J.* **2005**, *11*, 2471. (c) Krafft, M. E.; Boñaga, L. V. R.; Felts, A. S.; Hirosawa, C.; Kerrigan, S. *J. Org. Chem.* **2003**, *68*, 6039. (d) Shi, M.; Shao, L.-X.; Xu, B. *Org. Lett.* **2003**, *5*, 579.

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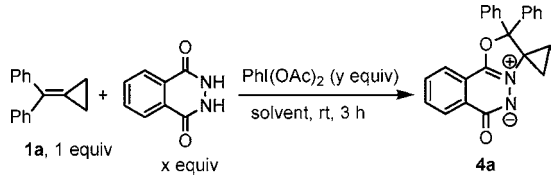
dition could take place. Herein, we wish to report iodobenzene diacetate-mediated 1,3-dipolar cycloaddition of MCPs **1**, vinylidenecyclopropanes (VCPs) **2**, and a MCB **3a** with phthalhydrazide under mild conditions, leading to some novel dihydrooxazole derivatives in good yields.

First, we utilized 1,1-diphenylmethylenecyclopropane **1a** as the substrate to examine the feasibility of the reaction. The results are summarized in Table 1. We found that the reaction proceeded smoothly in dichloromethane at room temperature to give the corresponding cycloaddition adduct **4a** as a new 1,3-dipole product in good yields within 3 h, and the best result was obtained when 1.2 equiv of iodobenzene diacetate and phthalhydrazide were used (Table 1, entry 2). The solvent effect was also investigated, and we found that **4a** could be isolated in good yields when 1,2-dichloroethane (DCE), chloroform, toluene, and acetonitrile were used as the solvents, but in low yields when tetrahydrofuran (THF) or diethyl ether was employed (Table 1, entries 5−10).

The structure of **4a** was confirmed by X-ray diffraction. The ORTEP drawing of **4a** is shown in Figure 1.[9]

Table 1. Iodobenzene Diacetate Mediated Cycloaddition of MCP **1a** (0.3 mmol) with Phthalhydrazide



entry	x	y	solvent	yield of **4a** [%][a]
1	1.0	1.0	CH_2Cl_2	78
2	1.2	1.2	CH_2Cl_2	88
3	1.5	1.5	CH_2Cl_2	84
4	2.0	2.0	CH_2Cl_2	82
5	1.2	1.2	DCE	88
6	1.2	1.2	$CHCl_3$	85
7	1.2	1.2	$PhCH_3$	87
8	1.2	1.2	CH_3CN	77
9	1.2	1.2	THF	25
10	1.2	1.2	Et_2O	15

[a] Isolated yields.

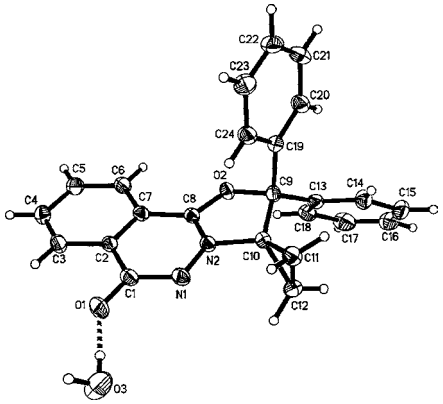


Figure 1. The X-ray crystal structure of **4a**.

With these optimized reaction conditions in hand, we next carried out iodobenzene diacetate-mediated 1,3-dipolar cycloadditions of MCPs **1b−q** with phthalhydrazide to determine the substrate scopes of this interesting reaction. We found that the corresponding dihydrooxazole derivatives **4b−q** were obtained in good yields (Table 2). The substituents on the MCPs could be an aryl group, a hydrogen atom, or a methyl group. In addition, neither electron-donating, electron-neutral, nor electron-withdrawing groups on the aromatic ring significantly affected the yields of the products.

Vinylidenecyclopropanes (VCPs)[10] **2** were also taken into the reaction and the corresponding cycloaddition products **5**

(4) Selected recent articles on MCPs: (a) Siriwardana, A. I.; Kamada, M.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 5932. (b) Nakamura, I.; Nemoto, T.; Yamamoto, Y.; de Meijere, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5176. (c) Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 10540. (d) Gulías, M.; García, R.; Delgado, A.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 384. (e) Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9282. (f) Rajamaki, S.; Kilburn, J. D. *Chem. Commun.* **2005**, 1637. (g) Patient, L.; Berry, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1015. (h) Scott, M. E.; Schwarz, C. A.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521. (i) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045. (j) Kamikawa, K.; Shimizu, Y.; Takemoto, S.; Matsuzaka, H. *Org. Lett.* **2006**, *8*, 4011. (k) Murakami, M.; Ishida, N.; Miura, T. *Chem. Commun.* **2006**, 643. (l) Yu, L.; Huang, X.; Xie, M. *Synlett* **2006**, 423. (m) Chen, W.; Huang, X.; Zhou, H.; Ren, L. *Synthesis* **2006**, 609. (n) Huang, X.; Fu, W. J. *Synthesis* **2006**, 1016. (o) Li, Q.; Shi, M.; Timmons, C.; Li, G. *Org. Lett.* **2006**, *8*, 625. (p) Shao, L. X.; Xu, B.; Huang, J. W.; Shi, M. *Chem. Eur. J.* **2006**, *12*, 510. (q) Shi, M.; Wang, B.-Y.; Huang, J.-W. *J. Org. Chem.* **2005**, *70*, 5606. (r) Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430. (s) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043.

(5) Selected recent examples, see: (a) Zanobini, A.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, 1251. (b) Revuelta, J.; Cicchi, S.; Brandi, A. *J. Org. Chem.* **2005**, *70*, 5636. (c) Cordero, F. M.; Salvati, M.; Pisaneschi, F.; Brandi, A. *Eur. J. Org. Chem.* **2004**, 2205. (d) Marradi, M.; Brandi, A.; de Meijere, A. *Synlett* **2006**, 1125. (e) Marradi, M.; Brandi, A.; Magull, J.; Schill, H.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, 5485 and references cited therein.

(6) Li, J.; Liang, J. L.; Chan, P. W. H.; Che, C. M. *Tetrahedron Lett.* **2004**, *45*, 2685 and references cited therein.

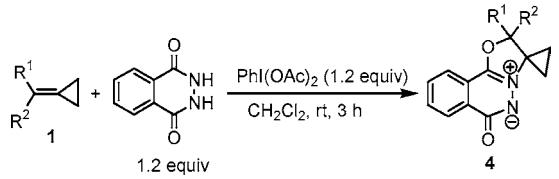
(7) (a) Krasnova, L. B.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 2011. (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194 and references cited therein.

(8) Liang, Y.; Jiao, L.; Wang, Y.; Chen, Y.; Ma, L.; Xu, J.; Zhang, S.; Yu, Z.-X. *Org. Lett.* **2006**, *8*, 5877.

(9) The crystal data of **4a** have been deposited in CCDC with number 622720. Empirical formula: $C_{24}H_{20}O_3N_2$. Formula weight: 384.42. Crystal color, habit: colorless, prismatic. Crystal dimensions: 0.480 × 0.337 × 0.180 mm^3. Crystal system: monoclinic. Lattice type: primitive. Lattice parameters: a = 9.0803(9) Å, b = 21.286(2) Å, c = 9.9234(9) Å, α = 90°, β = 101.687(2)°, γ = 90°, V = 1878.3(3) $Å^3$. Space group: $P2(1)/n$. Z = 4. D_{calc} = 1.359 g/cm^3. F_{000} = 808. Diffractometer: Rigaku AFC7R. Residuals: R, R_w 0.0470, 0.1026.

(10) Selected recent articles on VCPs, see: (a) Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H. *Chem. Lett.* **2000**, 1144. (b) Mizuno, K.; Maeda, H.; Sugita, H.; Nishioka, S.; Hirai, T.; Sugimoto, A. *Org. Lett.* **2001**, *3*, 581. (c) Mizuno, K.; Sugita, H.; Kamada, T.; Otsuji, Y. *Chem. Lett.* **1994**, 449. (d) Maeda, H.; Hirai, T.; Sugimoto, A.; Mizuno, K. *J. Org. Chem.* **2003**, *68*, 7700. (e) Shi, M.; Lu, J.-M. *J. Org. Chem.* **2006**, *71*, 1920. (f) Shi, M.; Lu, J.-M. *Synlett* **2005**, 2352. (g) Shi, M.; Ma, M.; Shao, L.-X. *Tetrahedron Lett.* **2005**, *46*, 7609. (h) Shi, M.; Lu, J.-M.; Xu, G.-C. *Tetrahedron Lett.* **2005**, *46*, 4745. (i) Xu, G.-C.; Ma, M.; Liu, L.-P.; Shi, M. *Synlett* **2005**, 1869. (j) Xu, G.-C.; Liu, L.-P.; Lu, J.-M.; Shi, M. *J. Am. Chem. Soc.* **2005**, *127*, 14552. (k) Shao, L.-X.; Zhang, Y.-P.; Qi, M.-H.; Shi, M. *Org. Lett.* **2007**, *9*, 117.

Table 2. Iodobenzene Diacetate Mediated Cycloadditions of MCPs **1** (0.3 mmol) with Phthalhydrazide

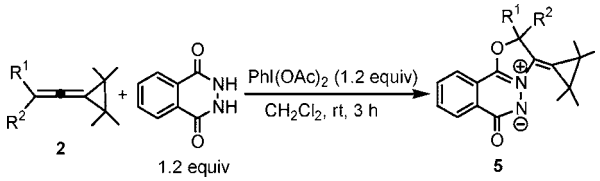


entry	R^1/R^2	yield of **4** [%][a]
1	*p*-$CH_3C_6H_4$/*p*-$CH_3C_6H_4$, **1b**	**4b**, 84
2	*p*-$CH_3OC_6H_4$/*p*-$CH_3OC_6H_4$, **1c**	**4c**, 87
3	*p*-ClC_6H_4/*p*-ClC_6H_4, **1d**	**4d**, 85
4	*p*-FC_6H_4/*p*-FC_6H_4, **1e**	**4e**, 86
5	*p*-$CH_3OC_6H_4$/C_6H_5, **1f**	**4f**, 86
6	*p*-ClC_6H_4/C_6H_5, **1g**	**4g**, 82
7	C_6H_5/H, **1h**	**4h**, 75
8	*o*-$CH_3C_6H_4$/H, **1i**	**4i**, 75
9	*m*-c$H_3C_6H_4$/H, **1j**	**4j**, 79
10	*p*-$CH_3C_6H_4$/H, **1k**	**4k**, 83
11	*p*-CH3OC_6H_4/H, **1*l***	**4*l***, 80
12	*o*-BnOC_6H_4/H, **1m**	**4m**, 73
13	*p*-ClC_6H_4/H, **1n**	**4n**, 79
14	*p*-BrC_6H_4/H, **1o**	**4o**, 81
15	C_6H_5/Me, **1p**	**4p**, 71
16	*o*-MeC_6H_4/Me, **1q**	**4q**, 82

[a] Isolated yields.

were obtained in good yields. The results are summarized in Table 3. In the reactions, the distal carbon−carbon double

Table 3. Iodobenzene Diacetate Mediated Cycloaddition of VCPs **2** (0.3 Mmol) with Phthalhydrazide



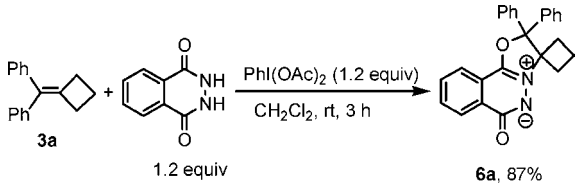
entry	R^1/R^2	yield of **5** [%][a]
1	C_6H_5/C_6H_5, **2a**	**5a**, 84
2	*p*-$CH_3C_6H_4$/*p*-$CH_3C_6H_4$, **2b**	**5b**, 87
3	*p*-ClC_6H_4/*p*-ClC_6H_4, **2c**	**5c**, 84
4	*p*-FC_6H_4/*p*-FC_6H_4, **2d**	**5d**, 86
5	*p*-ClC_6H_4/C_6H_5, **2e**	**5e**, 85

[a] Isolated yields.

bond from the cyclopropane was the reactive position. The structures of the products were determined by ^1H and ^{13}C NMR spectroscopic data and HRMS (see the Supporting Information).

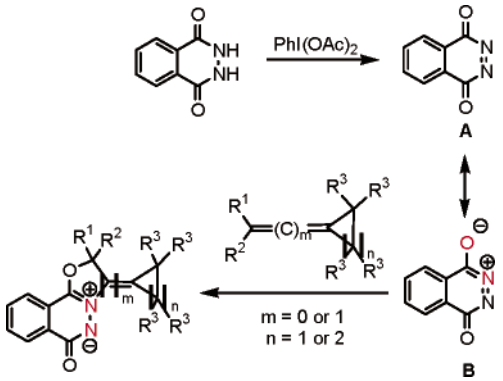
Afterward, a methylenecyclobutane (MCB) **3a** was also tested in the reaction, and the corresponding cycloaddition adduct **6a** was obtained in 87% yield under identical conditions (Scheme 1).

Scheme 1. Iodobenzene Diacetate Mediated Cycloaddition of MCB **3a** (0.3 Mmol) with Phthalhydrazide



The control experiment has confirmed that this 1,3-dipole cycloaddition reaction under these optimized conditions was unaffected by the addition of the radical inhibitors such as TEMPO and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (1.0 equiv), rendering unlikely the intervention of a radical pathway. Therefore, the mechanism of this novel 1,3-dipolar cycloaddition was described in Scheme 2. Iodobenzene

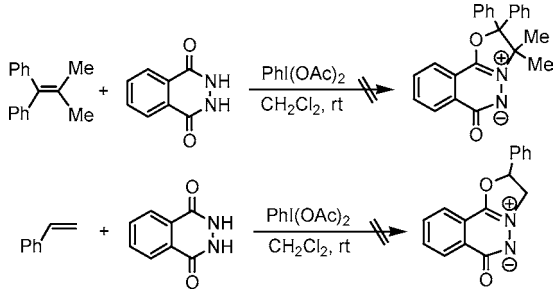
Scheme 2. A Plausible Reaction Mechanism



diacetate oxidized phthalhydrazide to phthalazine-1,4-dione **A**,[11] which was an equivalent of 1,3-dipole intermediate **B**.[12] The 1,3-dipole **B** reacted with the highly strained carbon−carbon double bond of MCP, VCP, and MCB to give the corresponding cycloaddition products.

To determine the scope and limitations of this novel cycloaddition, 2-methyl-1,1-diphenylpropene and styrene were taken into the reaction. However, unfortunately no cycloaddition product was formed under identical conditions

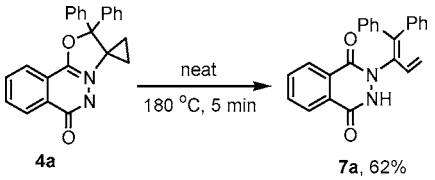
Scheme 3. Attempted Cycloaddition of General Alkenes



(Scheme 3). This result clearly suggests that a highly strained double bond is necessary for the reaction.

Furthermore, upon heating compound **4a** to 180 °C neat for 5 min, a rearranged product **7a** was isolated in 62% yield (Scheme 4).

Scheme 4. Transformation of Compound **4a** to **7a**



4a **7a**, 62%

In conclusion, we have found a novel 1,3-dipolar cycloaddition of MCPs, VCPs, and a MCB with phthalhydrazide under the promotion of iodobenzene diacetate to give the corresponding dihydrooxazole derivatives in good yields. A plausible reaction mechanism has been proposed on the basis of control experiments. Efforts are underway in the laboratory to further elucidate the mechanistic details of these reactions and to understand their scope and limitations.

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Supporting Information Available: The spectroscopic data (^{1}H, ^{13}C spectroscopic data), HRMS of the compounds shown in Tables 1−3 and Schemes 1−4, and the X-ray crystal structure of compound **4a** along with the detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Phthalhydrazide could be oxidized to phthalazine-1,4-dione by Pb(OAc)$_4$ or *N*-bromosuccinimide (NBS), see: (a) Contreras, F. G.; Lora-tamayo, M.; Sanz, A. M. *Heterocycles* **1987**, *25*, 193. (b) Contreras, F. G.; Lora-tamayo, M.; Sanz, A. M. *Heterocycles* **1989**, *28*, 791. (c) Coxon, J. M.; O' Connel, M. J.; Steel, P. J. *J. Org. Chem.* **1987**, *52*, 4726.

(12) Phthalazine-1,4-dione was often employed in aza-Diels−Alder reactions as the dienophile, see ref 11. To our best knowledge, however, there are no articles that reported it could react as a 1,3-dipole.