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Phosphine-Catalyzed [3+2] Annulation of Electron-Deficient Alkynes with *N*-Hydroxyphthalimide: Synthesis of 3a-Hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-ones

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Abstract: The phosphine-catalyzed [3+2] annulation of electron-deficient alkynes with *N*-hydroxyphthalimide has been developed to give a variety of pharmaceutically attractive 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-ones in good to excellent yields.

Keywords: [3+2] annulation reactions; electron-deficient alkynes; fused heterocycles; *N*-hydroxyphthalimide; nucleophilic phosphines

The development of competent methodologies to construct heterocyclic motifs is of great importance in both synthetic organic chemistry and medicinal chemistry due to their occurrence in a wide range of natural products and drugs.[1] Accordingly, a great deal of target-directed and diversity-oriented synthetic methods have been exploited for heterocycle synthesis.[2] Thus far, while the synthesis of heterocycles has been the subject of a large body of literature, the construction of highly functionalized nitrogen-containing fused heterocycles remains highly desirable, especially the synthesis of "drug-like" molecules.[3]

Nucleophilic phosphine-catalyzed reactions are among the most important methods available for ring construction.[4] Some famous examples include intermolecular double-Michael reactions of dinucleophiles with acetylenes or allenes,[5] annulation of Morita–Baylis–Hillman adduct carbonates with activated alkene,[6] cycloadditions of allenes to a wide range of polarized C=X bonds (X = N, O, and C),[7] annulations *via* the "Huisgen zwitterion".[8] Recently, intramolecular Morita–Baylis–Hillman reactions[9] and intramolecular Rauhut–Currier reactions[10] have also become an important tool for the synthesis of cyclic compounds. However, while the these reactions have been widely explored,[11] the electrophiles mainly include aldehydes, imines or activated ketones and no example of an amide was reported as an electrophile so far. While numerous examples of *N*-hydroxyphthalimide (NHPI) being used as a catalyst for the oxidation of certain types of hydrocarbons can be found,[12] there are no examples of *N*-hydroxyphthalimide being used in phosphine-catalyzed annulation reactions with activated alkynes. Herein, we wish to report novel examples of the phosphine-catalyzed [3+2] annulation reactions of *N*-hydroxyphthalimide (NHPI) with electron-deficient alkynes for the construction of the pharmaceutically attractive nitrogen-containing fused heterocycle derivatives – 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-ones[13] – and also showcase an example of the development for the Morita–Baylis–Hillman reactions with amides as electrophile partners of MBH reactions.

At the outset of our study, we first chose ethyl propiolate (**1a**) and *N*-hydroxyphthalimide (**2**) as the standard substrates to search for suitable reaction conditions for the synthesis 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-one derivatives, and the results are shown in Table 1. The reaction of **1a** with **2** in the presence of Ph_3P (20 mol%) in CH_2Cl_2 at room temperature for 6 h afforded **3a** as a white solid in 51% yield (entry 1, Table 1), and this compound was characterized by ^1H and ^{13}C NMR spectroscopy and HR-MS analysis. Subsequently, Bu_3P with relatively stronger nucleophilicity was tested in the reaction and it afforded the product **3a** in comparable yield, but no product was obtained when the weaker nucleophilic trimethyl phosphite was used as catalyst in place of Ph_3P in CH_2Cl_2 (entries 2 and 3, Table 1). The yield of **3a** could be improved by heating CH_2Cl_2 at reflux, but it decreased sharply when the reaction was car-

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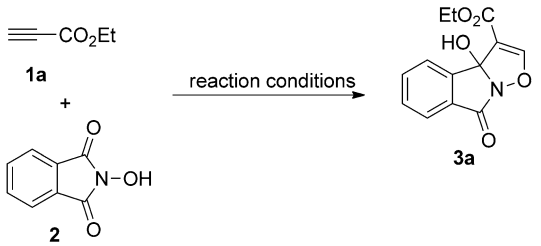
Table 1. Optimization of the reaction conditions for **3a**.[a]



Entry	Catalyst	Solvent	T [°C]	t [h]	Yield [%][b]
1	Ph_3P	CH_2Cl_2	r.t.[c]	6	51
2	Bu_3P	CH_2Cl_2	r.t.	6	48
3	$P(OMe)_3$	CH_2Cl_2	r.t.	6	0
4	Ph_3P	CH_2Cl_2	reflux	6	65
5	Bu_3P	CH_2Cl_2	reflux	6	58
6	Ph_3P	CH_2Cl_2	0	6	42
7	Bu_3P	CH_2Cl_2	0	6	31
8	Ph_3P	Et_2O	reflux	6	60
9	Ph_3P	acetone	60	6	36
10	Ph_3P	THF	60	6	0
11	Ph_3P	toluene	60	6	31
12	Ph_3P	CH_3CN	60	1	32
13	Ph_3P	DMF	60	1	70
14	Ph_3P	DMF	r.t.	1	99
15	Ph_3P	DMF	0	6	88
16[d]	Ph_3P	DMF	r.t.	6	83
17[e]	Ph_3P	DMF	r.t.	6	trace
18[f]	Ph_3P	DMF	r.t.	6	80

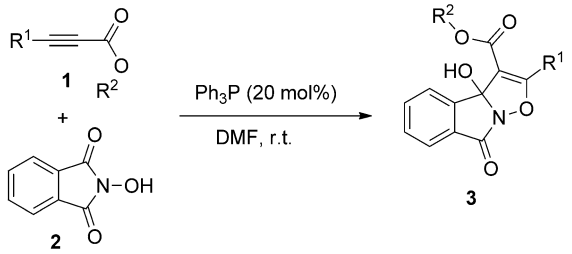
[a] Unless noted otherwise, the reaction of ethyl propiolate **1a** (0.6 mmol), *N*-hydroxyphthalimide **2** (0.5 mmol) and catalyst (20 mol%) was performed in 1 mL of solvent under N_2.
[b] Isolated yield based on **2**.
[c] r.t. = room temperature.
[d] 10 mol% of Ph_3P were used.
[e] No catalyst was used.
[f] 5 mol% of Ph_3P were used.

ried out at 0 °C in the presence of either Ph_3P or Bu_3P in CH_2Cl_2 (entries 4–7, Table 1). Solvent screening revealed a significant solvent effect. Et_2O also led to the target product **3a** in moderate yield, while its kindred solvent-THF delivered no product at all (entries 8 and 10, Table 1).

When shifting the solvent to acetone, toluene, or CH_3CN, **3a** was obtained in 36, 31 or 32% yield, respectively (entries 9, 11 and 12, Table 1). DMF gave the best result for **3a** with respect to the reaction time as well as the yield (entry13, Table 1). Therefore, reaction temperature and catalyst amount were further examined in DMF (entries 14–18, Table 1). Lowering the reaction temperature to room temperature led to a better yield in DMF. However, on further decreasing the temperature to 0 °C, the yield decreased slightly, even with a prolonged reaction time of 6 h. Decreasing the loading of the catalyst PPh_3 to 10 mol% or 5 mol% did affect the reaction rate and the yield to a certain extent. Only a trace of product was found in the absence of PPh_3, which further showed the importance of Ph_3P for this transformation. Thus, we established the optimal reaction conditions for the effective construction of 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-one derivatives **3** as follows: use of 20 mol% PPh_3 as the catalyst and DMF as the solvent to perform the reaction at room temperature.[14]

Following the above optimized conditions, we first investigated a range of alkynoates As depicted in Table 2 all tested terminal alkynoates were found to be applicable to this reaction to give products **3** in good to excellent yields under the optimized reaction conditions. The nature of the substituent on the benzene ring of the benzyl propiolate had a slight impact on the yields. For example, for substrates with a methyl or methoxy group attached on the benzene ring, the corresponding products were obtained in yields of 89% and 99%, respectively (entries 4 and 6, Table 2). Substrates with a Cl or nitro group on the benzene ring also gave the desired products in the ex-

Table 2. Synthesis of 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8-(3a*H*)-one derivatives **3** from alkynoates **1** and *N*-hydroxyphthalimide **2**.[a]



Entry	R^1	R^2	3	Yield [%][b]
1	H	Et	**3a**	99
2	H	Me	**3b**	99
3	H	$PhCH_2$	**3c**	95
4	H	4-Me-C_6H_4-CH_2	**3d**	89
5	H	4-MeS-C_6H_4-CH_2	**3e**	92
6	H	4-MeO-C_6H_4-CH_2	**3f**	99
7	H	4-F-C_6H_4-CH_2	**3g**	99
8[c]	H	4-Cl-C_6H_4-CH_2	**3h**	96
9[c]	H	4-NO_2-C_6H_4-CH_2	**3i**	94
10	H	1-naphthyl-CH_2	**3j**	96
11[d]	H	2-furyl-CH_2	**3k**	90
12	Me	Et	**3l**	55 (99)[e]
13[e]	*n*-hexyl	Et	**3m**	trace (83)[e]
14	Ph	Et	**3n**	99

[a] Unless noted otherwise, the reactions were performed on a 0.5-mmol scale with 1.2 equiv. of **1**, 1.0 equiv. of **2** and 20 mol% of Ph_3P in 1 mL DMF at room temperature under N_2 for 1 h.
[b] Isolated yield based on **2**.
[c] For 6 h.
[d] For 0.75 h.
[e] 20 mol% of Bu_3P were used

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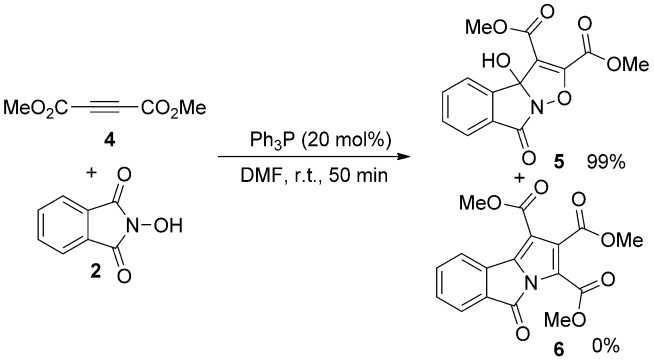
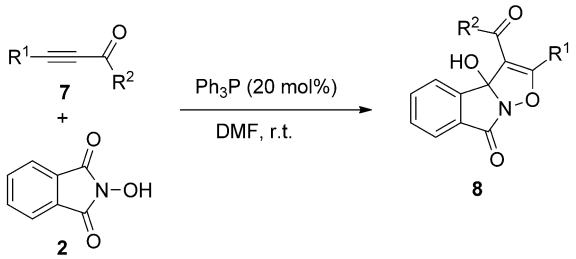
cellent yields, although the a longer reaction time was needed. (entries 8 and 9, Table 2). To our delight, naphthalen-1-ylmethyl propiolate as well as furan-2-ylmethyl propiolate also reacted smoothly with **2** to give the desired 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8-(3a*H*)-one derivatives in excellent yields (entries 10 and 11, Table 2). It is worth mentioning here that, under the above conditions, ethyl 2-butynoate and ethyl 3-phenylpropiolate could also react with **2** to furnish the corresponding 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-one derivatives **3l** and **3n** in the yields of 55% and 99%, respectively (entries 12 and 14, Table 2). To our disappointment, only a trace of target product was formed when ethyl non-2-ynoate was applied in the reaction (entry 13, Table 2). Happily, ethyl non-2-ynoate could give the target product in good yield when Bu_3P was used as catalyst in place of Ph_3P. And it was nice to see that ethyl 2-butynoate could also give a better result in the presence of Bu_3P than that in the presence of Ph_3P. It is highlighted here that dimethyl acetylenedicarboxylate **4** gave the corresponding product **5** in the yield of 99% under our reaction conditions; while Yavari et al. reported that dimethyl acetylenedicarboxylate **4** in the presence of a stoichiometric amount of triphenylphosphine at room temperature in CH_2Cl_2 yielded a pyrroloisoindole derivative **6**,[15] which suggested that our reaction conditions played an important role in the present annulation reaction (Scheme 1).



Scheme 1. Dimethyl acetylenedicarboxylate **4** as substrate.

To further broaden the scope of this phosphine-catalyzed protocol, we also investigated a range of alkynyl ketones (Table 3). In the case of the reaction of but-3-yn-2-one with **2**, under the standard conditions, the target product **8a** was obtained in 57% yield and a large amount of **2** was not consumed. However, the product **8a** was obtained in an excellent yield of 96% after increasing the amount of but-3-yn-2-one to 3 equiv. (entry 1, Table 3). The standard conditions proved general for aromatic alkynyl ketones. For example, when 1-phenylpropynone and 4-phenylbut-3-yn-2-one were treated with **2**, 3a-hydroxyisoxazolo-

Table 3. Synthesis of 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8-(3a*H*)-one derivatives **8** from alkynyl ketones **1** and *N*-hydroxyphthalimide **2**.[a]



Entry	R^1	R^2	8	Yield [%][b]
1[c]	H	Me	**8a**	57 (96)[d]
2	H	Ph	**8b**	99
3	Ph	Me	**8c**	99
4	Ph	Ph	**8d**	99
5	Ph	4-F-C_6H_4	**8e**	99
6	Ph	4-Cl-C_6H_4	**8f**	99
7[e]	Ph	4-MeO-C_6H_4	**8g**	74
8	Ph	3,4-$(MeO)_2C_6H_3$	**8h**	84
9[c]	Ph	3-pyridyl	**8i**	74
10[c]	n-Pr	Ph	**8j**	99

[a] Unless noted otherwise, the reactions were performed on a 0.5-mmol scale with 1.2 equiv. of **7**, 1.0 equiv. of **2** and 20 mol% of Ph_3P in 1 mL of DMF at room temperature under N_2 for 1 h.
[b] Isolated yield based on **2**.
[c] For 6 h.
[d] 3 equiv. of but-3-yn-2-one were used.
[e] For 2 h.

[3,2-*a*]isoindol-8(3a*H*)-one derivatives **8b** and **8c** were obtained in excellent yields, respectively (entries 2 and 3, Table 3). Screening revealed that several substituents, such as F, Cl, and MeO, on the aryl ring of the internal alkyne were well tolerated, but the yields decreased clearly when MeO was present on the aryl ring of the internal alkyne (entries 4–8, Table 2). Notably, 3-phenyl-1-pyridin-4-ylpropynone was also compatible with the standard reaction conditions but gave a decreased yield (entry 9, Table 3). An alkyl-substituted alkynyl ketone like 1-phenylhex-2-yn-1-one also successfully underwent annulation to give **8j** in an excellent yield.[16]

The structures of the products were undeniably confirmed by X-ray crystallographic analyses of the compounds **8b**[17] and **8c**.[18] The ORTEP diagram of **8b** is shown in Figure 1.

Mechanistically, a suggested catalytic cycle for this unexpected [3+2] annulation of electron-deficient alkynes with *N*-hydroxyphthalimide (NHPI) has been proposed (Scheme 2).[9b] The reaction could be triggered by the nucleophilic addition of Ph_3P to the electron-deficient carbon-carbon triple bond of **1a** to produce zwitterion **I**, which can then deprotonate *N*-hydroxyphthalimide (NHPI) **2** to generate intermediates

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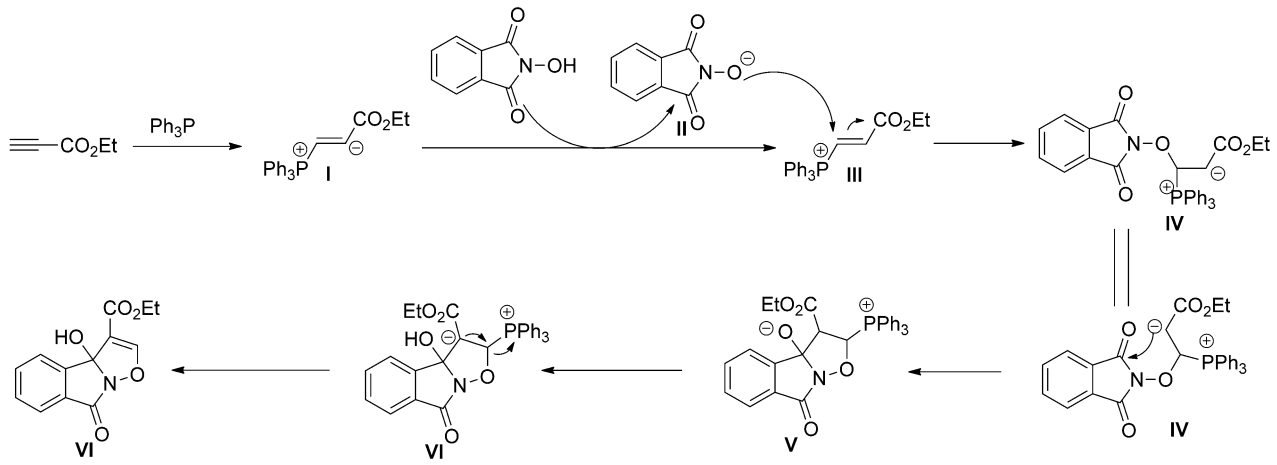

Scheme 2. Proposed mechanism for PPh_3-catalyzed [3+2] annulation of electron-deficient alkynes with *N*-hydroxyphthalimide.

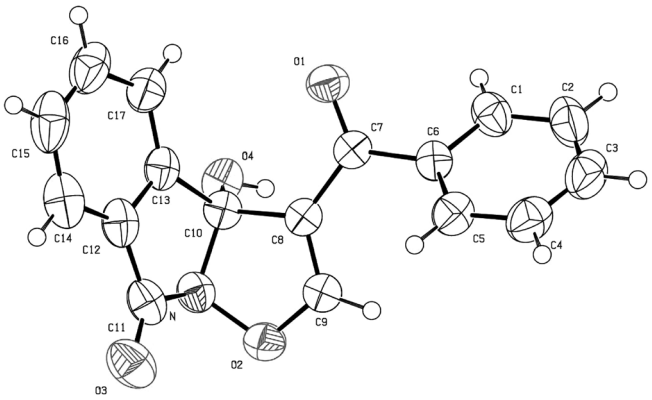

Figure 1. X-ray crystal structure of **8b**.

II and **III**. Intermediate **II** then undergoes Michael addition to **III** to give **IV**.[19] Intermediate **IV** might then undergo intramolecular nucleophilic attack to form intermediate **V**, followed by proton transfer and elimination of Ph_3P to produce the desired product **3a**.

In conclusion, a novel and efficient [3+2] annulation of electron-deficient alkynes with *N*-hydroxyphthalimide (NHPI) has been developed by using Ph_3P as catalyst. With the application of this synthetic method, a series of 3a-hydroxyisoxazolo[3,2-*a*]isoindol-8(3a*H*)-one derivatives was prepared in good to excellent yields under mild reaction conditions. This protocol is associated with readily available starting materials, mild conditions, high yields and wide range of synthetic potential of the product. Especially, the structures of these products may be attractive for potential drug discovery. The potential utilization and extension of the scope of the methodology and the examination of the biological activity of the products are the subject of ongoing studies in our laboratory.

Experimental Section

General Experimental Procedure

To a solution of the electron-deficient alkyne (0.6 mmol) and *N*-hydroxyphthalimide (81.5 mg, 0.5 mmol) in dry DMF (1 mL) was added Ph_3P (26.2 mg, 0.1 mmol) or Bu_3P (20.0 mg, 0.1 mmol). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for the required period of time. After completion of the reaction as monitored by TLC, the reaction mixture was diluted with CH_2Cl_2, and was washed with water and brine successively, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash chromatography (SiO_2; ethyl acetate/PE, 1:10~1:3) yielded the desired products.

Ethyl 3a-hydroxy-8-oxo-3a,8-dihydroisoxazolo[3,2-*a*]isoindole-3-carboxylate (3a): Yield: 129.2 mg (99%); white solid; mp 74–75 °C; IR (KBr): $\nu = 3417, 3086, 2983, 1791, 1741, 1707, 1683, 1649, 1614, 1467, 1371, 1182, 1087, 1057, 879, 696\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.01$ (d, $J = 7.7$ Hz, 1H), 7.77 (d, $J = 7.6$ Hz, 1H), 7.72 (dd, $J = 7.6$, 1.0 Hz, 1H), 7.61 (s, 1H), 7.54 (dd, $J = 7.6$, 0.8 Hz, 1H), 4.53 (brs, 1H), 4.25–4.19 (m, 1H), 4.19–4.13 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.94, 162.05, 159.13, 145.89, 135.69, 130.68, 128.31, 126.23, 125.01, 112.13, 95.80, 61.08, 14.28$; HR-MS (ESI): $m/z = 262.0711$, calcd. for $C_{13}H_{12}NO_5$ $[M+H]^+$: 262.0710.

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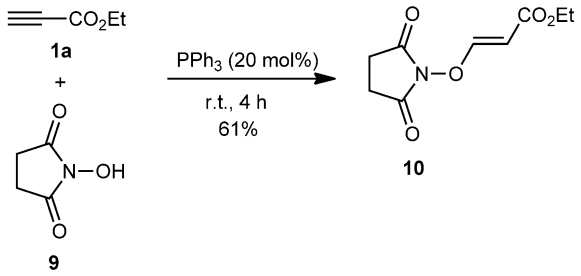

[17] CCDC 932873 (**8b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[18] CCDC 937934 (**8c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
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