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Construction of Heterocyclic Compounds by Use of α-Diazophosphonates: New One-Pot Syntheses of Indoles and Isocoumarins

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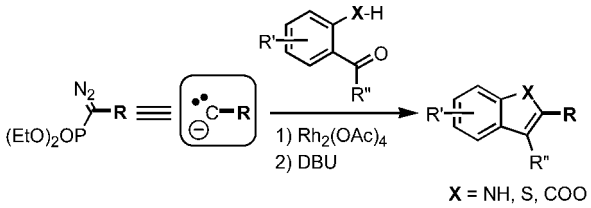
ABSTRACT



α-Diazophosphonates, which have extremely useful properties from a synthetic point of view, are disclosed as 1,1-ambiphilic one-carbon building blocks for one-pot construction of various heterocyclic compounds. They are easily prepared and have higher stability by the effect of the phosphoryl group than corresponding α-diazocarbonyl compounds. Using this synthon, we have developed a novel, mild, and efficient synthetic method of 2,3-disubstituted indoles and 3,4-disubstituted isocoumarins.

It is an attractive and versatile synthetic method to create several bonds utilizing the multifunctional building blocks bearing more than one reactive functional group in the same molecule. In particular, molecules having reaction centers on the same carbon atom can be employed to construct cyclic compounds with one carbon homologation. The Simmons−Smith cyclopropanation[1] and isoquinoline syntheses reported by Sekine[2] and Silveira[3] are categorized as this type of reaction.

The transition-metal-catalyzed decomposition of diazo compounds has become a standard method in organic synthesis.[4] Rhodium(II) complexes, first described by Teissié et al.,[5] have been proven to be the most versatile catalysts for the decomposition of α-diazocarbonyl compounds and are now widely used in transformations such as C−H insertion, X−H insertion (X = NH, O, S), cyclopropanation, and ylide formation. In contrast to the α-diazocarbonyl compounds, α-diazophosphonates **1** have been much less widely studied so far.[6] Moody et al. reported a new, efficient synthesis of cyclic ethers based on the rhodium carbenoids derived from **1**.[7] From a synthetic point of view, α-diazophosphonates have extremely useful properties, e.g., unique structural features having two different kinds of functional groups on the same carbon atom, higher stability by the effect of the phosphoryl group than that of corresponding α-dia-

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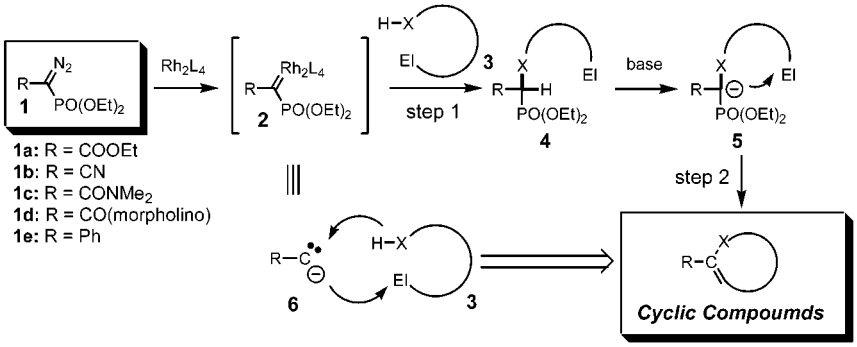
Scheme 1



zocarbonyl compounds,[8] and ease of preparation. Thus, we planned to utilize α-diazophosphonates **1** as the building blocks for the construction of various heterocycles via dirhodium(II) complex catalyzed heteroatom-H insertion and the subsequent intramolecular Horner−Wadsworth−Emmons (HWE) reaction.

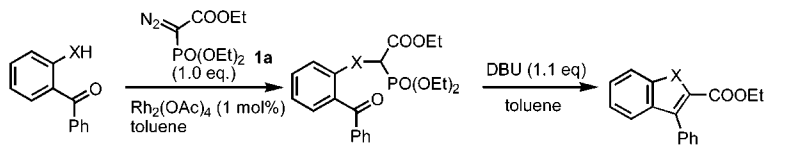
α-Phosphoryl metallocarbenoid **2**, which is easily generated from **1** in the presence of dirhodium(II) complex, can be regarded as one carbon synthon **6** that has the potentiality of reacting with both nucleophiles (X−H) and electrophiles (El) on the same carbon atom (Scheme 1). Our strategy is based upon the initial intermolecular X−H insertion reaction of **1** with the compounds **3** having both X−H and El groups (step 1) and the subsequent cyclization of phosphonate stabilized carbanion **5** under the basic conditions (step 2) to give cyclic compounds.

To make the scope and limitation of this methodology clear, we examined the reaction of triethyl diazophosphonoacetate **1a** with 2-aminobenzophenone **7a**, 2-hydroxybenzophenone **10**, 2-thiobenzophenone **13**, or 2-benzoylbenzoic acid **16a** (Scheme 2). In our initial attempt, rhodium(II) acetate-catalyzed reaction of **1a** with **7a** in toluene at 80 °C gave the corresponding N−H insertion product **8a** in 86% yield. The experimental procedure of **8a** was quite simple since the slow addition of **1a** to the reaction mixture was not necessary, in contrast to the case of cyclic ether formation reported by Fuchs.[9] The subsequent treatment of **8a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature in toluene gave indole **9a** quantitatively as shown in Scheme 2. While the S−H insertion reaction of **1a** with **13** and the subsequent cyclization gave benzothiophene **15** in 44% yield, no O−H insertion product **11** was obtained from **10**. These results are consistent with the previous findings[6b] that the yields of the O−H insertion reaction of phenol derivatives bearing an electron-withdrawing group or a bulky group on the ortho position are generally low. Surprisingly, treatment of 2-benzoylbenzoic acid **16a** with **1a** in the presence of 1 mol % of rhodium(II) acetate at 80 °C in toluene afforded the desired compound **17a** quantitatively. To our knowledge, this is the first example of the rhodium(II) acetate-catalyzed insertion reaction of diazocompounds into the O−H bond of the carboxy group. The subsequent intramolecular HWE reaction of **17a** with DBU at room temperature in toluene smoothly proceeded to give the ethyl 4-phenylisocoumarin-3-carboxylate **18a** in 81% yield.

The indole nucleus is widely present in numerous natural products and biologically active compounds, and the synthesis of indoles has attracted considerable interest in synthetic organic chemistry for many years.[10] However, few efficient synthetic methods for the construction of 2,3-disubstituted indoles are available despite many reports for the synthetic methods of indoles. On the other hand, isocoumarins, which display a wide range of biological activities,[11] are a class of naturally occurring lactones and are used as intermediates for the synthesis of isoquinolinones.[12] Thus, we selected indole and isocoumarin derivatives as target compounds in order to exhibit the usefulness of this synthetic methodology.

In the course of our study on the synthesis of indole derivatives, we next turned our attention to the development of one-pot procedures without the isolation of **8** in order to make the procedures as simple as possible and to avoid

Scheme 2

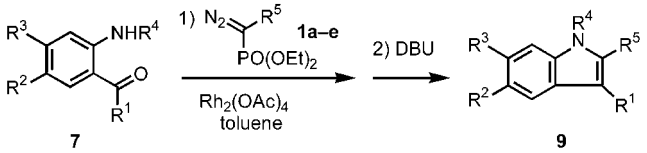


7a: X = NH
10: X = O
13: X = S
16a: X = COO

8a: X = NH (86%)
11: X = O (0%)
14: X = S (not isolated)
17a: X = COO (quant)

9a: X = NH (99%)
12: X = O
15: X = S (44% from **13**)
18a: X = COO (81%)

Table 1. One-Pot Preparation of Indoles[a]



7 9

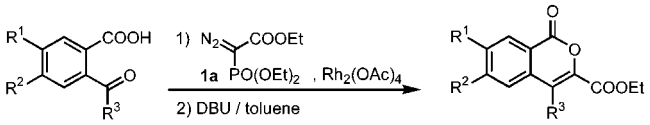
entry	compd 7	R^1	R^2	R^3	R^4	R^5	product 9	yield[b] (%)
1	**7a**	Ph	H	H	H	COOEt	**9a**	86
2	**7b**	H	H	H	H	COOEt	**9b**	73
3	**7c**	Me	H	H	H	COOEt	**9c**	84
4	**7d**	CH_2Ph	H	H	H	COOEt	**9d**	84
5	**7e**	Ph	Cl	H	H	COOEt	**9e**	91
6	**7f**	Ph	NO_2	H	H	COOEt	**9f**	84
7	**7g**	2-thienyl	OMe	OMe	H	COOEt	**9g**	72
8	**7a**	Ph	H	H	H	CN	**9h**	91
9[c]	**7a**	Ph	H	H	H	$CONMe_2$	**9i**	76
10[c]	**7a**	Ph	H	H	H		**9j**	56
11[d]	**7a**	Ph	H	H	H	Ph	**9k**	14
12	**7h**	Ph	Cl	H	Me	COOEt	**9l**	20

[a] Rh-catalyzed reactions were run with 1.0 equiv of amino ketone, 1.0 equiv of α-diazophosphonate, and 1.0 mol % of $Rh_2(OAc)_4$ in toluene at 80 °C. Cyclization reactions were run with 1.1 equiv of DBU in toluene at room temperature unless otherwise stated. [b] Yields are isolated yields. [c] Cyclization reaction was carried out at 80 °C. [d] LiHMDS was employed in the cyclization reaction.

material loss during the workup procedures. As shown in Table 1, **9a** was obtained in 86% yield from the starting material **7a** in one-pot procedures (entry 1), almost the same yield as with the stepwise procedures (Scheme 2).

2-Aminobenzaldehyde was transformed into ethyl indole-2-carboxylate **9b** in 73% yield (Table 1, entry 2). Enolizable ketones such as methyl and benzyl ketone were successfully employed to give the desired 3-alkylindoles in good yields (Table 1, entries 3 and 4). It is noteworthy that both electron-withdrawing and electron-donating groups on the phenyl ring of aniline are tolerated in this reaction (Table 1, entries 5−7). It should be noted that the resultant indole 2-carboxylate derivatives could be considered to be the stable equivalents of 2-unsubstituted indoles, since the indoles are stabilized by the electron-withdrawing effect of the ester group, and these compounds may be decarboxylated on heating.[13] In terms of the substituents of the α-diazophosphonates, electron-withdrawing groups such as the ester or cyano groups facilitated the cyclization to indoles enough to proceed at room temperature (Table 1, entries 1−8), while the cyclization of the compounds bearing the tertiary amide group required relatively high temperature. 3-*N*,*N*-Dimethylcarbamoyl and 3-morpholinocarbonyl derivatives (**9i** and **9j**) were obtained by heating at 80 °C in 76% and 56% yields, respectively. On the other hand, the yield of 2-phenylindole **9k** from α-diazobenzylphosphonate **1e** was very low even when treated with a strong base, lithium hexamethyldisilazide (LiHMDS). These results indicate that the yields of the cyclization reaction are highly dependent upon the acidity of the active methylene group of the insertion

Table 2. One-Pot Preparation of Isocoumarins[a]

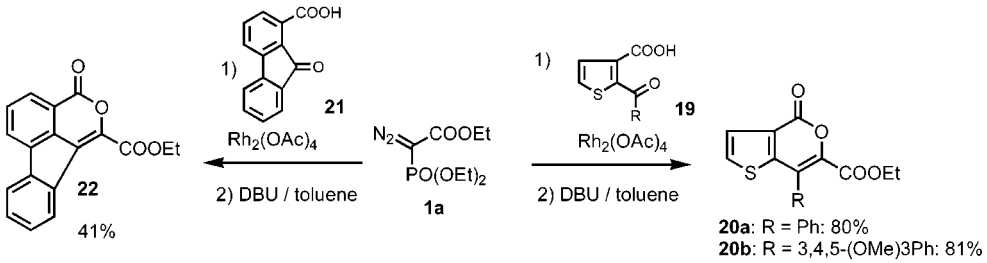


16 18

entry	compd 16	R^1	R^2	R^3	product 18	yield[b] (%)
1	**16a**	H	H	Ph	**18a**	81
2	**16b**	H	H	H	**18b**	54
3	**16c**	OMe	OMe	3,4,5-$(OMe)_3$Ph	**18c**	73
4	**16d**	OCH_2Ph	H	3,4,5-$(OMe)_3$Ph	**18d**	73

[a] Rh-catalyzed reactions were run with 1.0 equiv of carboxylic acid, 1.0 equiv of α-diazophosphonate, and 1.0 mol % of $Rh_2(OAc)_4$ in toluene at 80 °C. Cyclization reactions were run with 1.1 equiv of DBU in toluene at room temperature. [b] Yields are isolated yields.

Scheme 3



products. The N−H insertion reaction of **7h** having the *N*-methylamino group was less successful, probably due to the steric hindrance of the methyl group that prevents the coordination of the nitrogen atom to the rhodium metal of the phosphorylcarbenoid (Table 1, entry 12).

Table 2 summarizes the results of the one-pot synthesis of isocoumarins by the reaction of **1a** with carboxylic acids **16**. Ethyl 4-phenylisocoumarin-3-carboxylate **18a** was obtained in 81% yield by the one-pot procedures without the isolation of **17a** (Table 2, entry 1). In general, 4-aryl derivatives were obtained in good yields (Table 2, entries 3 and 4), but the yield of 4-unsubstituted derivative dropped off (Table 2, entry 2). It is noteworthy that 4-(3,4,5-trimethoxyphenyl) derivatives **18c** and **18d** were successfully obtained, since the concomitant formation of demethylated compounds were observed under the Chatterjea's conditions (strong acidic conditions), which is the most common method for the preparation of this class of compounds.[14]

Then we explored a further application to isocoumarin-related ring systems (Scheme 3). The thieno[3,2-*c*]pyran derivative **20**, which could not be synthesized by Chatterjea's method in our attempts, was successfully obtained by our synthetic method. Moreover, highly strained 2-oxa-fluoranthene **22** was also formed in 41% yield from 9-fluorenone-1-carboxylic acid **21** in one-pot procedures.

In summary, we have proposed the novel usage of α-diazophosphonates **1** as one carbon synthon **6** having both nucleophilic and electrophilic character on the same carbon for one-pot construction of various heterocycles. Based on this concept, we have developed the novel, mild, and efficient synthetic method of 2,3-disubstituted indoles and 3,4-disubstituted isocoumarins. Application of our method to the synthesis of other types of heterocycles is currently underway in our laboratories.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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