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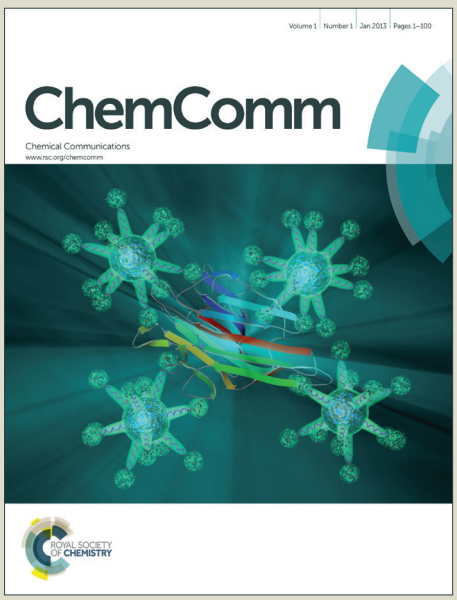

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COMMUNICATION

The Use of the Mitsunobu Reagent for the Formation of Heterocycles: a Simple Method for the Preparation of 3-Alkyl-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones from Carboxylic Acids

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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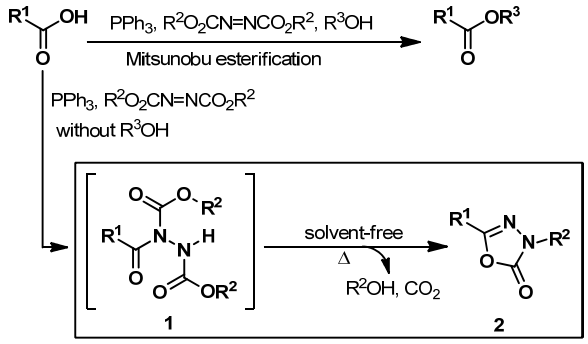
The reaction of carboxylic acids with Mitsunobu reagents, prepared by the reaction of triphenylphosphine with dialkyl azodicarboxylates, followed by heating at 180–190 °C under solvent-free conditions, afforded 3-alkyl-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones. This facile and convenient method readily provides the 1,3,4-oxadiazolone ring-system in good yields using a one-pot protocol starting from the corresponding carboxylic acids. It was also demonstrated that the presence of catalytic base facilitates the final ring closure forming the 1,3,4-oxadiazol-2(3*H*)-one.

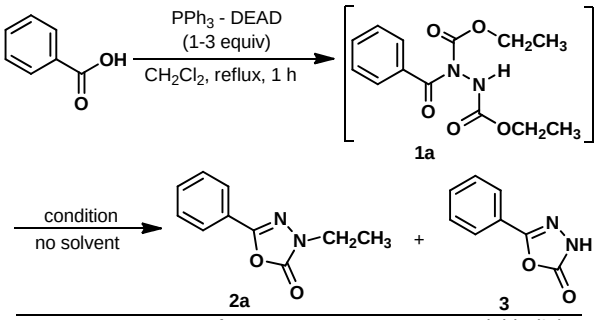
The Mitsunobu reaction[1–3] is a useful method for esterification of carboxylic acids under neutral conditions. The Mitsunobu reagent is used as an activating agent and is prepared by the reaction of phosphines with azodicarboxylic acid diesters. Hughes et al.[4] have reported that the reaction of a carboxylic acid with triphenylphosphine (PPh_3) and diisopropyl azodicarboxylate in the absence of an alcohol leads to the formation of the corresponding 1-acylhydrazine-1,2-dicarboxylates **1** as the major product. During the course of our studies, the observation was made that heating a reaction mixture containing **1** under solvent-free conditions afforded 3-alkyl-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones **2** (Scheme 1).



Scheme 1 One-pot formation of 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones (**2**)

The development of an efficient method for preparing 3-substituted 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones is desirable as these compounds exhibit a variety of biological activities including maxi-K channel opening,[5] MAO inhibition,[6] and fungicidal activity.[7] Some progress has been made in developing procedures for the synthesis of 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones.[5–14] However, these procedures involve many steps and require the use of hazardous reagents. In this communication we report a facile one-pot synthesis of 3-alkyl-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones arising from the corresponding carboxylic acids under solvent-free conditions. In initial studies, the reaction of benzoic acid was explored with respect to the equivalents (1–3 equiv) of the Mitsunobu reagent, which was prepared by the reaction of PPh_3 with diethyl azodicarboxylate (PPh_3–DEAD) (Table 1).

Table 1

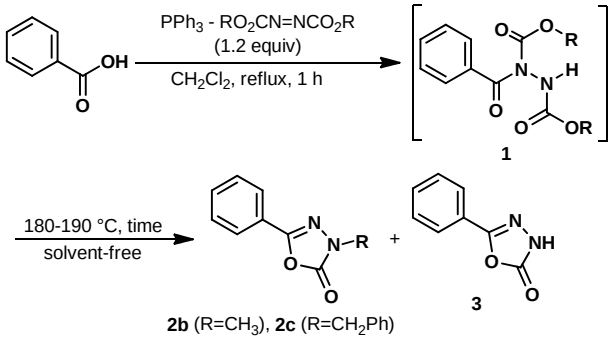


Entry	Amount of PPh_3–DEAD (equiv)	Condition	Yields (%) 1a	2a	3
1	1.2	room temperature	72	0	0
2	1.2	140–150 °C, 24 h	0	55	8
3	1	180–190 °C, 24 h	0	65	6
4	1.2	180–190 °C, 24 h	0	71	3
5	1.5	180–190 °C, 24 h	0	77	0
6	2	180–190 °C, 24 h	0	73	0
7	3	180–190 °C, 22 h	0	50	0
8	1.2	180–190 °C, 6 h	0	70	0
9	1.2	180–190 °C, 2 h	0	69	0

The reaction of benzoic acid with PPh_3–DEAD (1.2 equiv) in CH_2Cl_2 under reflux for 1 h provided diethyl 1-benzoylhydrazine-1,2-dicarboxylate (**1a**) in 72% yield (entry 1); this result was identical to that reported by Hughes et al.[4] In contrast, heating at 140–150 °C for 24 h under solvent-free conditions afforded 3-ethyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**2a**) and 5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**3**) in 55% and 8% yields, respectively (entry 2). It was subsequently found that the yield of **2a** could be increased by heating the reaction mixture containing **1a** at 180–190 °C. Varying the equivalents of the Mitsunobu reagent (1 , 1.2, 1.5, and 2 equivs of PPh_3–DEAD) in CH_2Cl_2 under reflux for 1 h followed by heating at 180–190 °C for 24 h afforded **2a** in 65%, 71%, 77%, and 73% yields, respectively (entries 3–6). However, when 3 equiv of PPh_3–DEAD was used, the yield of **2a** was slightly diminished (entry 7). It was found that the reactions at 180–190 °C for a shorter time (6 h and 2 h) compared to the reaction for 24 h (entry 4) gave similar yields (70% and 69%; entries 8 and 9).

Next, the reactions of benzoic acid with various Mitsunobu reagents, PPh_3–DMAD (dimethyl ester), PPh_3–DBAD (dibenzyl ester), PPh_3–DIAD (di-*i*-propyl ester), and PPh_3–D*t*BAD (di-*t*-butyl ester), were carried out to test the effect of the alkyl substituent on the cyclization event (Table 2). A mixture of benzoic acid was treated with 1.2 equiv of the respective Mitsunobu reagent in CH_2Cl_2 under reflux for 1 h, followed by heating under solvent-free conditions at 180–190 °C for the time period depicted in Table 2. Using PPh_3–DMAD as the Mitsunobu reagent (180–190 °C, 2 h) provided 3-methyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**2b**) in 66% yield (entry 1). When the reaction time was extended to 24 h, the yield dropped to 62% (entry 2). With PPh_3–DBAD, 3-benzyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**2c**) was likewise obtained, in 52% yield (entry 3). In contrast, the PPh_3–DIAD system did not provide 3-isopropyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**2d**) in appreciable yield (entries 4–6). This result was mirrored when the di-*t*-butyl azodicarboxylate (PPh_3–D*t*BAD) was employed (entry 7). These results may suggest that steric hindrance of the alkyl group on the ester moiety affects the reactivity of the cyclization. With smaller alkyl groups (*i.e.*, ethyl, methyl, and benzyl) the reaction proceeded smoothly to afford the 5-phenyl-1,3,4-oxadiazol-2(3*H*)-ones (**2a**-**2c**) in good yields.

Table 2

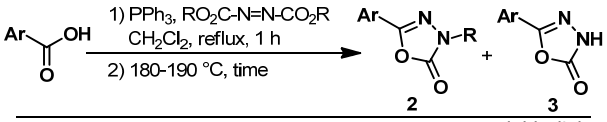


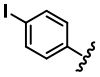
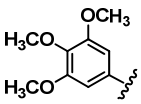
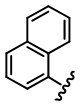
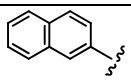
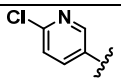
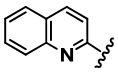
2b (R=CH_3), **2c** (R=CH_2Ph)
2d (R=$CH(CH_3)_2$), **2e** (R=$C(CH_3)_3$)

Entry	Mitsunobu reagent	R	Time (h)	Yields (%) 2b-2e	3	1
1	PPh_3–DMAD	CH_3	2	66 (**2b**)	5	
2	PPh_3–DMAD	CH_3	24	62 (**2b**)	4	
3	PPh_3–DBAD	CH_2Ph	2	52 (**2c**)	13	
4	PPh_3–DIAD	$CH(CH_3)_2$	2	0 (**2d**)	0	62
5	PPh_3–DIAD	$CH(CH_3)_2$	24	10 (**2d**)	34	
6	PPh_3–DIAD	$CH(CH_3)_2$	48	5 (**2d**)	29	
7	PPh_3–DtBAD	$C(CH_3)_3$	19	0 (**2e**)	7	

The scope of the reaction was next explored by varying the aromatic carboxylic acid in combination with the Mitsunobu reagents (Table 3). 4-Iodobenzoic acid (entries 1–6), 3,4,5-trimethoxybenzoic acid (entries 7–11), 1-naphthoic acid (entries 12–17), 2-naphthoic acid (entries 18 and 19), 2-pyridinecarboxylic acid (entries 20–24), 2-chloropyridine-5-carboxylic acid (entries 25 and 26), 4-pyridinecarboxylic acid (entry 27), and 2-quinolinecarboxylic acid (entries 28–32) were tested as substrates with the PPh_3–DMAD, PPh_3–DEAD, PPh_3–DBAD, and PPh_3–DIAD Mitsunobu reagents.

Table 3



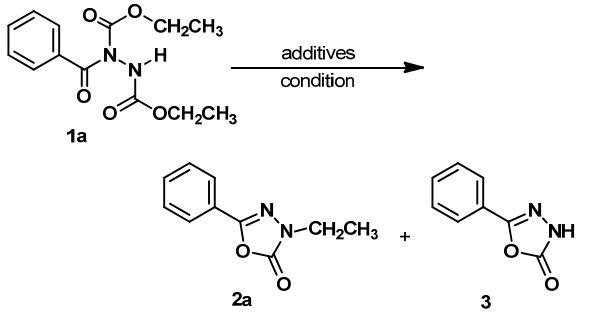
Entry	Ar	Mitsunobu reagent	R	Time (h)	Yields (%) 2	3
1		PPh_3–DMAD	CH_3	2	77	0
2		PPh_3–DEAD	CH_2CH_3	5	43	23
3		PPh_3–DEAD	CH_2CH_3	24	50	24
4		PPh_3–DBAD	CH_2Ph	2	72	0
5		PPh_3–DIAD	$CH(CH_3)_2$	24	25	48
6		PPh_3–DIAD	$CH(CH_3)_2$	48	24	14
7		PPh_3–DMAD	CH_3	2	80	0
8		PPh_3–DEAD	CH_2CH_3	4	64	0
9		PPh_3–DBAD	CH_2Ph	2	64	0
10		PPh_3–DIAD	$CH(CH_3)_2$	24	21	19
11		PPh_3–DIAD	$CH(CH_3)_2$	48	9	39
12		PPh_3–DMAD	CH_3	2	42	5
13		PPh_3–DMAD	CH_3	24	64	0
14		PPh_3–DEAD	CH_2CH_3	2	54	0
15		PPh_3–DEAD	CH_2CH_3	5	48	0
16		PPh_3–DBAD	CH_2Ph	2	61	0
17		PPh_3–DIAD	$CH(CH_3)_2$	24	8	48
18		PPh_3–DEAD	CH_2CH_3	2	70	7
19		PPh_3–DEAD	CH_2CH_3	24	57	4
20		PPh_3–DMAD	CH_3	2	76	0
21		PPh_3–DEAD	CH_2CH_3	4	62	0
22		PPh_3–DBAD	CH_2Ph	2	76	0
23		PPh_3–DIAD	$CH(CH_3)_2$	24	21	0
24		PPh_3–DIAD	$CH(CH_3)_2$	48	12	0
25		PPh_3–DEAD	CH_2CH_3	2	38	0
26		PPh_3–DEAD	CH_2CH_3	19	25	0
27		PPh_3–DEAD	CH_2CH_3	19	40	0
28		PPh_3–DMAD	CH_3	2	79	0
29		PPh_3–DEAD	CH_2CH_3	2	70	0
30		PPh_3–DBAD	CH_2Ph	2	63	14
31		PPh_3–DIAD	$CH(CH_3)_2$	24	13	27
32		PPh_3–DIAD	$CH(CH_3)_2$	48	8	0

Overall, the generation of the desired product, **2**, smoothly proceeded when Mitsunobu reagents with smaller alkyl groups such as methyl, ethyl, and benzyl were used. As was previously the case, the reaction using PPh_3–DIAD as the reagent afforded **2** in low yield.

These results are consistent with those depicted in Table 2, and highlight the structure–reactivity relationship of the Mitsunobu reagent with respect to the size of the alkyl group on the azodicarboxylate.

The conversion of purified intermediate **1a** under several conditions was next carried out in order to identify whether the cyclization event was occurring thermally, or was perhaps facilitated by the reaction conditions (Table 4).

Table 4

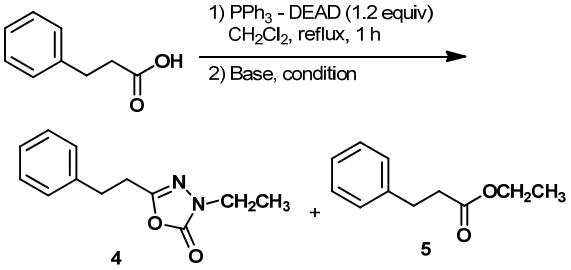


Entry	Additive or solvent	Condition	Yields (%)		
			2a	**3**	**1a**
1	none	180–190 °C, 5 h	0	0	41
2	none	180–190 °C, 24 h	0	0	0
3	diglyme	reflux, 17 h	0	0	49
4	mesitylene	reflux, 17 h	0	0	24
5	PPh_3–DEAD (1 equiv)	180–190 °C, 5 h	54	12	0
6	PPh_3–DEAD (1 equiv)	180–190 °C, 18 h	39	23	0
7	PPh_3–DEAD (0.2 equiv)	180–190 °C, 23 h	51	20	0
8	PPh_3–DEAD (0.05 equiv)	180–190 °C, 19 h	49	17	0
9	O=PPh_3 (1 equiv)	180–190 °C, 5 h	11	0	0
10	$EtO_2CNHNHCO_2Et$ (0.2 equiv)	180–190 °C, 24 h	0	0	0
11	EtONa (0.1 equiv)	180–190 °C, 4 h	15	21	0
12	EtONa (0.03 equiv)	180–190 °C, 2 h	42	27	0
13	NaH (1 equiv)	180–190 °C, 5 h	16	0	0
14	NaH (0.1 equiv)	180–190 °C, 2 h	48	15	0
15	DBU (0.07 equiv)	180–190 °C, 2 h	64	4	0

Interestingly, heating **1a** at 180–190 °C without additives provided no desired product **2a** (entries 1 and 2). Similarly, heating **1a** in the neutral organic solvents, diglyme (bp. 162 °C) or mesitylene (bp. 163–166 °C), under reflux for 17 h did not lead to the formation of **2a** (entries 3 and 4). It was surmised that the conversion of **1a** into **2a** requires not only heating, but is also facilitated by the Mitsunobu reaction conditions. It can be presumed that the presence of a reagent used in this reaction, such as PPh_3–DEAD, or the by-products triphenylphosphine oxide (O=PPh_3) or diethyl 1,2-hydrazinedicarboxylate ($EtO_2CNHNHCO_2Et$), may accelerate the formation of **2a**. As expected, when a mixture of **1a** and 1 equiv of PPh_3–DEAD was heated at 180–190 °C, **2a** was obtained in 54% (for 5 h) and 39% (for 18 h) yield, respectively (entries 5 and 6). It should be noted that a catalytic amount of PPh_3–DEAD (0.2 equiv or 0.05 equiv) also promoted the cyclization (entries 7 and 8). The use of O=PPh_3 slightly promoted the reaction, affording **2a** in 11% yield (entry 9). However, heating **1a** with 0.2 equiv of $EtO_2CNHNHCO_2Et$ at 180–190 °C for 24 h did not lead to the formation of **2a** (entry 10). It was speculated that reaction of benzoic acid with PPh_3–DEAD first provides **1a**, which is subsequently converted into **2a**. This conversion is facilitated by the presence of a base and heating. To test this hypothesis, a mixture of **1a** and one of several bases such as EtONa (entries 11 and 12), NaH (entries 13 and 14), and DBU (entry 15), was heated at 180-190 °C, effecting the formation of **2a**. It was also found that the yield of **2a** was increased by using a catalytic amount of base.

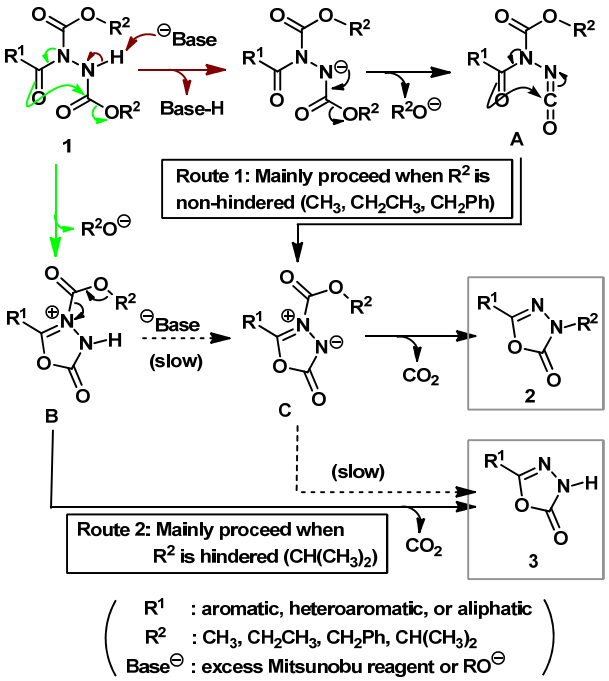
Reactions using an aliphatic carboxylic acid as a substrate were examined (Table 5). A mixture of 3-phenylpropionic acid and PPh_3–DEAD (1.2 equiv) in CH_2Cl_2 was heated to reflux for 1 h, followed by removal of CH_2Cl_2 and heating with or without a base. The reaction in the absence of a base afforded the corresponding cyclized product (**4**) in 17% yield (entry 1). On the other hand, the yield of **4** was elevated by using a catalytic amount of base such as EtONa (entry 2) or DBU (entries 3 and 4). The use of a stoichiometric amount of base (1 equiv DBU) resulted in a lower yield (entry 5). In one-pot cyclizations using an aromatic carboxylic acid as a substrate (*e. g.*, Table 1, Table 3), the Mitsunobu reagent (*e. g.*, excess PPh_3–DEAD) acts as a base, so the addition of exogenous base is not required.

Table 5



Entry	Base	Condition	Yields (%)	
			4	**5**
1	none	180-190 °C, 24 h	17	0
2	EtONa (0.05 equiv)	180-190 °C, 4 h	32	25
3	DBU (0.09 equiv)	140-150 °C, 6 h	32	28
4	DBU (0.09 equiv)	180-190 °C, 24 h	40	14
5	DBU (1 equiv)	180-190 °C, 6 h	26	21

A reasonable mechanism for the cyclization/alkyl group migration is depicted in Scheme 2. Two different routes are probable for the generation of **2** and **3**. When an alkyl group R^2 is non-hindered (methyl, ethyl, and benzyl), the NH proton in **1** is deprotonated to generate an isocyanate **A**, which is cyclized (**C**). Rearrangement of R^2 then proceeds to form **2**. On the other hand, when R^2 is hindered, as is the case with an isopropyl group, **1** cannot be deprotonated due to hindrance by R^2. Therefore, cyclization proceeds and forms B, followed by decomposition of an ester moiety to give **3**. The generated R^2O^- shown in this mechanism acts as a base catalytically.



Scheme 2 Proposed mechanism for the generation of 3-alkyl-5-(hetero)aryl-1,3,4-oxadiazol-2(3*H*)-ones and 5-(hetero)aryl-1,3,4-oxadiazol-2(3*H*)-ones **B** and **C**

In summary, an efficient and operationally simplified method for the preparation of 3-alkyl-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones from carboxylic acids has been developed. These studies revealed that a catalytic amount of a basic additive is required to convert the intermediate alkyl 1-aroylhydrazine-1,2-dicarboxylates into the corresponding 3-alkyl-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones at 180–190 °C.

Notes and references

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† All yields shown in the tables are isolated yields. Typical experimental procedure: Azodicarboxylic acid ester was added dropwise to a mixture of carboxylic acid and PPh_3 in CH_2Cl_2 at rt, then the mixture was heated to reflux for 1 h. After CH_2Cl_2 was removed at atmospheric pressure, the residue was heated at 180-190 °C, followed by purification with silica gel column chromatography to give the desired product.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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