

# ADDP and PS-PPh<sub>3</sub>: an efficient Mitsunobu protocol for the preparation of pyridine ether PPAR agonists

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## Preliminary Communication

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## Abstract

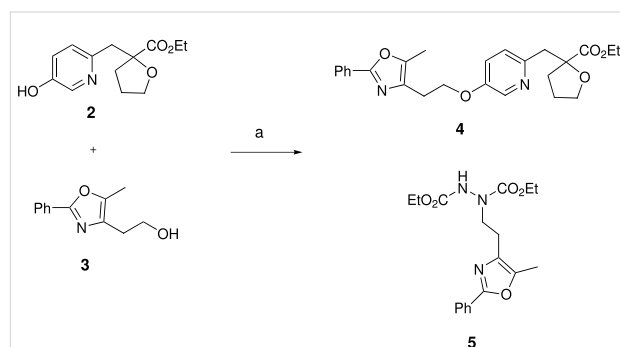
A series of pyridine ether PPAR agonists were synthesized through an ADDP and PS-PPh<sub>3</sub> modified Mitsunobu protocol, which eliminated significant by-product formation. This method proved to be versatile, efficient and amenable to parallel synthesis.

## Findings

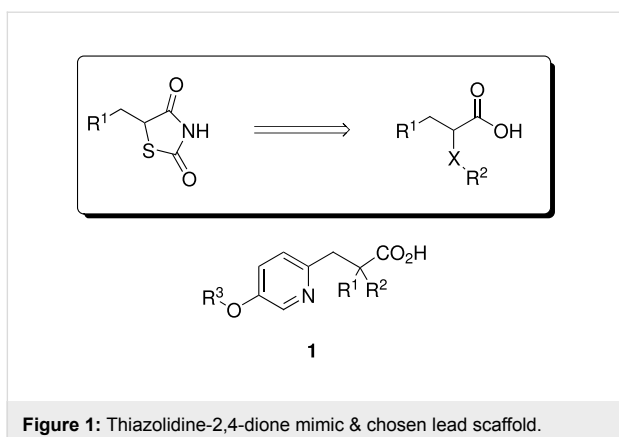
Peroxisome proliferator-activated receptors (PPARs) are pharmaceutical targets of great importance. Their wide-ranging effects on key transcriptional pathways for lipid handling, insulin sensitivity, inflammation and other functions have led to marketed drugs and vast clinical and preclinical research efforts.[1-11]

In 1991, a series of PPAR analogues were disclosed, which for the first time did not contain a thiazolidine-2,4-dione pharmacophore.[12] These were propanoic acid derivatives with  $\alpha$ -substitution to collectively serve as a mimic for the thiazolidine-2,4-dione ring. Based on the above and a knowledge of PPAR ligands publicly disclosed, we wished to synthesize compounds represented by the general structure **1** (Figure 1). Aromatic ethers are structural motifs found in many naturally occurring molecules and compounds of medicinal interest.[13] We envisaged the pyridyl ether moiety of **1** to be efficiently formed via

Mitsunobu coupling of the requisite pyridinol and alkyl alcohols.[14-17]



**Scheme 1:** Reagents and conditions: (a) PS-PPh<sub>3</sub>, DEAD, THF, rt, 16 h, 54%.



**Figure 1:** Thiazolidine-2,4-dione mimic & chosen lead scaffold.

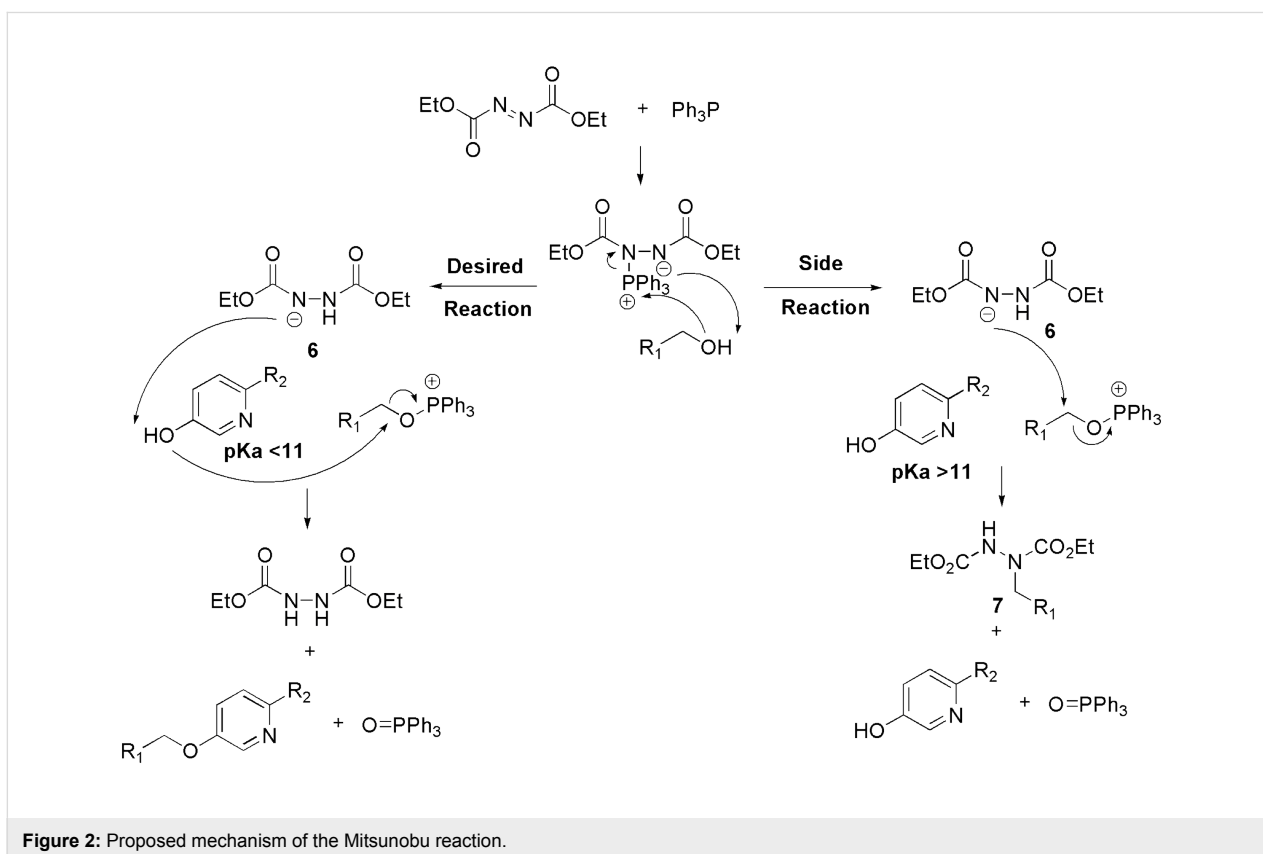
Our first attempt at the Mitsunobu reaction between pyridinol **2** and alcohol **3**, utilizing a modification of the conditions originally reported by Mitsunobu,[18] afforded pyridyl ether **4** in 54% yield (Scheme 1). Interestingly, the reaction did not reach completion and pyridinol **2** was recovered, despite the fact that it was the limiting reagent. Upon closer examination, compound **5** was observed as a major by-product (46% based on **3**).

By-products analogous to **5** have been observed in the literature when diethyl azodicarboxylate (DEAD) is used in certain Mitsunobu reactions.[18,19] This by-product formation is

believed to be dependent on the  $pK_a$  of the acidic component (e.g. **2**).[18] If the phenol has a  $pK_a > 11$ , the yield is considerably lower; and with the phenol having  $pK_a > 13$ , the desired reaction does not occur. The hydrazo anion **6**, in these cases, attacks the alkoxyphosphonium directly to afford alkylated hydrazine derivative **7** as the by-product (side reaction in Figure 2),[19] since anion **6** is not efficient in deprotonating the weakly acidic phenol.

One way to improve the above redox system is to enhance the basicity of anion **6** by the replacement of the alkoxy group OEt in DEAD with strong electron donating groups such as  $NR_2$ . [16] Thus, 1,1'-(azodicarbonyl)dipiperidine (ADDP),[20] 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD),[21] and  $N,N,N',N'$ -tetramethylazodicarboxamide (TMAD)[22] have been developed as new reagents in combination with tributyl phosphine (TBP).

We initially chose ADDP, due to its commercial availability and low cost. The original reference utilized ADDP and TBP in benzene,[20] but due to safety and ease of handling we chose to keep PS- $PPH_3$  and THF. Our first attempt was successful and no by-product **8** was observed in the reaction (Scheme 2) [see Supporting Information File 1 and Supporting Information File 2]. With the above result in hand, we then pursued a variety of



**Figure 2:** Proposed mechanism of the Mitsunobu reaction.

**Table 1:** Modified Mitsunobu coupling of pyridinol **2** and a variety of primary alcohols<sup>a</sup>

Entry	Alcohol	Product	Yield (%)	Entry	Alcohol	Product	Yield (%)
1		<b>9</b>	81	7		<b>15</b>	79
2		<b>10</b>	78	8		<b>16</b>	85
3		<b>11</b>	80	9		<b>17</b>	77
4		<b>12</b>	83	10		<b>18</b>	80
5		<b>13</b>	71	11		<b>19</b>	72
6		<b>14</b>	81	12		<b>20</b>	76

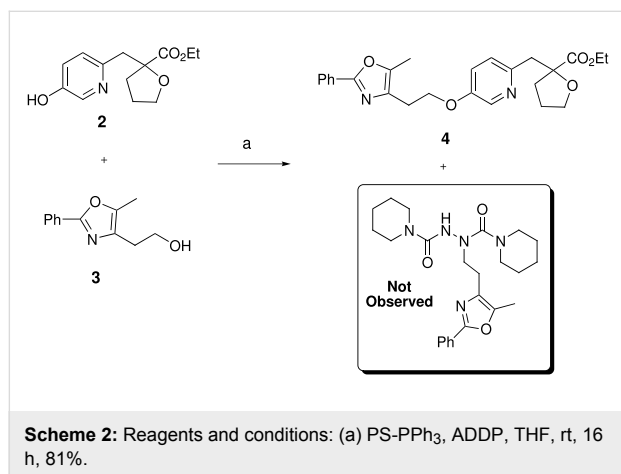
<sup>a</sup> Reactions were run using 0.5 mmol pyridinol, 0.55 mmol alcohol, 0.75 mmol PS-PPh<sub>3</sub>, 0.75 mmol ADDP and 5.5 mL tetrahydrofuran.

**Table 2:** Modified Mitsunobu coupling of alcohol **3** and a variety of pyridinols<sup>a</sup>

Entry	Pyridinol	Product	Yield (%)	Entry	Pyridinol	Product	Yield (%)
1		<b>21</b>	86	3		<b>23</b>	84
2		<b>22</b>	95	4		<b>24</b>	78

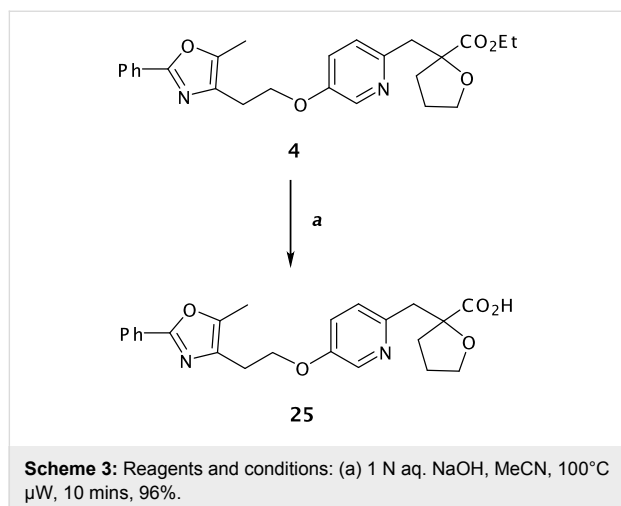
<sup>a</sup> Reactions were run using 0.5 mmol pyridinol, 0.55 mmol alcohol, 0.75 mmol PS-PPh<sub>3</sub>, 0.75 mmol ADDP and 5.5 mL tetrahydrofuran.

targets by performing the modified Mitsunobu reaction of **2** and a variety of primary alcohols (Table 1). In general, a variety of diverse alcohols afforded the expected products in excellent yield. As expected, oxazoles, thiazoles, pyrazoles, and pyridines are tolerated in this chemistry. In a limited number of cases, functionality (*e.g.* basic amines, benzimidazoles, indoles, etc.) caused no reaction to occur and only recovered starting materials were isolated (data not shown).



We then shifted our attention to variation of the pyridinol, whilst holding constant the 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethanol reactant **3** (Table 2). As expected, variation of the 2-substituent of the pyridine ring resulted in equally high yields.

Having efficiently synthesized a diverse set of intermediate esters, we then sought an expedient method for obtaining the final carboxylic acids. We opted for a microwave-assisted procedure for this basic hydrolysis step. As shown in Scheme 3, the carboxylic acids (*e.g.* **25**) could be obtained in a matter of minutes [see Supporting Information File 1 and Supporting



Information File 2]. The significant reduction in reaction time resulted in a productivity enhancement due to increased sample processing. A number of the other esters described in this manuscript were also subjected to these conditions and all afforded the pure carboxylic acids in 82–100% yield.

In summary, we have developed a modified Mitsunobu protocol utilizing 1,1'-(azodicarbonyl)dipiperidine (ADDP) and polymer-supported triphenylphosphine (PS-PPh<sub>3</sub>). Employment of this method resulted in a rapid, convenient, and high-yielding two step protocol for the preparation of PPAR agonists. In particular, the modified Mitsunobu coupling of pyridinols and alcohols proved to be versatile, efficient and amenable to parallel synthesis. A full account of the medicinal chemistry of these compounds will be given elsewhere.

## Supporting Information

### Supporting Information File 1

Supporting Information. Experimental procedures and data for all novel compounds described in this manuscript. [<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-2-21-S1.doc>]

### Supporting Information File 2

Auxiliary Data. Auxiliary data for all novel compounds described in this manuscript. [<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-2-21-S2.tiff>]

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