Synlett Y.-J. Huang et al. Letter

Silver-Catalyzed [3+3] Annulation of Glycine Imino Esters with Seyferth–Gilbert Reagent To Access Tetrahydro-1,2,4-triazine-carboxylate Esters

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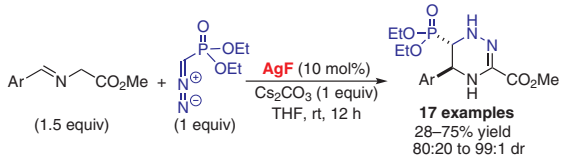

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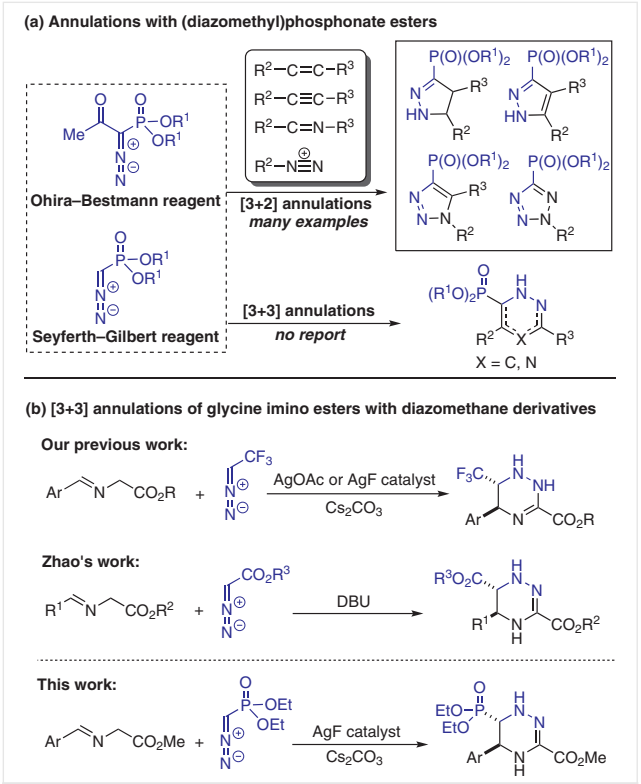
Abstract A silver-catalyzed protocol for [3+3] annulation of glycine imino esters with Seyferth–Gilbert reagent was developed. A variety of phosphorylated tetrahydro-1,2,4-triazinecarboxylate esters were synthesized in moderate to good yields and with excellent diastereoselectivities. The dehydrogenation of a tetrahydro-1,2,4-triazine product to the corresponding triazine counterpart was also demonstrated.

Key words [3+3] annulation, glycine imino esters, Seyferth–Gilbert reagent, triazines, phosphorylation

Phosphorylated nitrogenous heterocyclic compounds are prevalent biologically active compounds in medicinal chemistry,[1] important structural motifs in materials science,[2] and valuable intermediates for synthesizing ligands for catalysis.[3] Among the various methods available for their synthesis, two classes of (diazomethyl)phosphonate esters,[4] the Ohira–Bestmann[5] and the Seyferth–Gilbert reagents,[6] have proven to be versatile reagents for accessing a broad range of phosphorylated five-membered nitrogenous heterocycles,[7–11] such as pyrazolines,[7] pyrazoles,[8] triazolines,[9] or tetrazoles,[10] through [3+2]-annulation strategies (Scheme 1a; top). In sharp contrast, the synthesis of phosphorylated six-membered nitrogenous heterocycles based on these two phosphorylated diazomethane reagents remains undeveloped, probably due to a lack of suitable reaction substrates for [3+3] annulations (Scheme 1a; bottom). Recently, our group[12] and Zhao's group[13] discovered that glycine imino esters can serve as reliable substrates for the synthesis of functionalized tetrahydro-1,2,4-triazines through Ag-catalyzed annulation with 2-diazo-1,1,1-trifluoroethane (Scheme 1b; top) or base-promoted annulation with a diazoacetate ester (Scheme 1b; middle).



Scheme 1 Synthesis of phosphorylated heterocycles by [3+2]- and [3+3]-annulation strategies

As part of our continuing efforts in heterocycle synthesis based on diazomethane moieties,[10,12,14,15] we surmised that such a Ag-catalyzed protocol might also be viable in the synthesis of various six-membered heterocycles by using other diazomethane entities. Here, we describe the implementation of a Ag-catalyzed [3+3]-annulation reaction of glycine imino esters with Seyferth–Gilbert reagent

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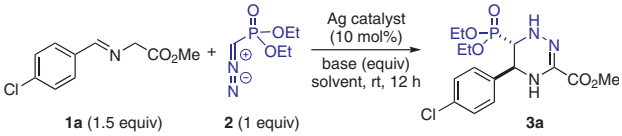
(Scheme 1b; bottom). This method provides ready access to phosphorylated tetrahydro-1,2,4-triazine carboxylic esters as a novel class of six-membered nitrogenous heterocyclic compounds.

We commenced our study by using methyl 2-[(4-chlorobenzylidene)amino]acetate (**1a**, 1.5 equiv) and Seyferth–Gilbert reagent (**2**; 1 equiv, 0.2 mmol) as model substrates (Table 1). In the presence of DBU as a base additive, **1a** underwent annulation with **2** in THF at room temperature in 12 hours, delivering the 1,4,5,6-tetrahydro-1,2,4-triazine-3-carboxylate ester **3a** as the desired product (entry 1). On switching the base to Cs_2CO_3 (1 equiv) and adding $AgNO_3$ as a catalyst, the yield of **3a** increased to 56% (entry 2). Neither the use of other carbonate bases nor conducting the reaction at 0 °C gave any **3a** (entries 3–5). Additionally, the yield was not enhanced when an excess of the Seyferth–Gilbert reagent was used (entry 6). Subsequently, AgF was found to be the optimal catalyst, slightly enhancing the yield to 57% (entries 7–13). Whereas the use of other solvents did not increase the yield (entries 14–19), a larger scale of the reaction substrates based on 0.3 mmol of **2** resulted in the formation of **3a** in 73% yield (entry 20), presumably due to a relative reduction in losses of the very polar triazine product.

With the optimized reaction conditions in hand (Table 1, entry 20), we proceeded to study the substrate scope of the annulation of glycine imino esters **1** with Seyferth–Gilbert reagent **2** (Scheme 2). This protocol permitted annulations with various glycine imino esters **1** bearing electron-withdrawing (**3a**–**h**), electron- donating (**3i**–**m**), or electron-neutral aryl groups (**3n**) to afford the corresponding phosphorylated tetrahydro-1,2,4-triazine-carboxylate esters **3**. Whereas the use of **1** containing electron-withdrawing aryl groups generally afforded the corresponding products in moderate to good yields, the presence of electron-donating or electron-neutral groups mostly led to the formation of **3** in modest yields. Noteworthily, the diastereoselectivities toward the phosphorylated tetrahydro-1,2,4-triazine products were particularly high, generally ranging from 94:6 to >99:1. In addition, a wide range of functional groups were compatible, including chloro (**3a**, **3d**), bromo (**3b**), fluoro (**3c**), ester (**3e**), nitro (**3f**), trifluoromethyl (**3g**), cyano (**3h**), and dialkylamino groups (**3l**). Moreover, 2- and 1-naphthyl (**3o**, **3p**) or anthracen-9-yl (**3q**) groups could be incorporated into the tetrahydro-1,2,4-triazine products. The relative configuration of the phosphorylated 1,2,4-tetrahydrotriazinecarboxylate ester products was further characterized by X-ray crystallographic analysis of **3b**.[16]

Interestingly, the triazines formed in Zhao's protocol and in the present protocol, which contain a 6-ester group and a 6-phosphoryl group, respectively, have different tautomeric structures to those of the products from our previous protocol, which contained a 6-trifluoromethyl group (Scheme 1). Presumably, the more-electron-withdrawing

Table 1 Optimization of [3+3] Annulation of a Glycine Imino Esters with Seyferth–Gilbert Reagent[a]



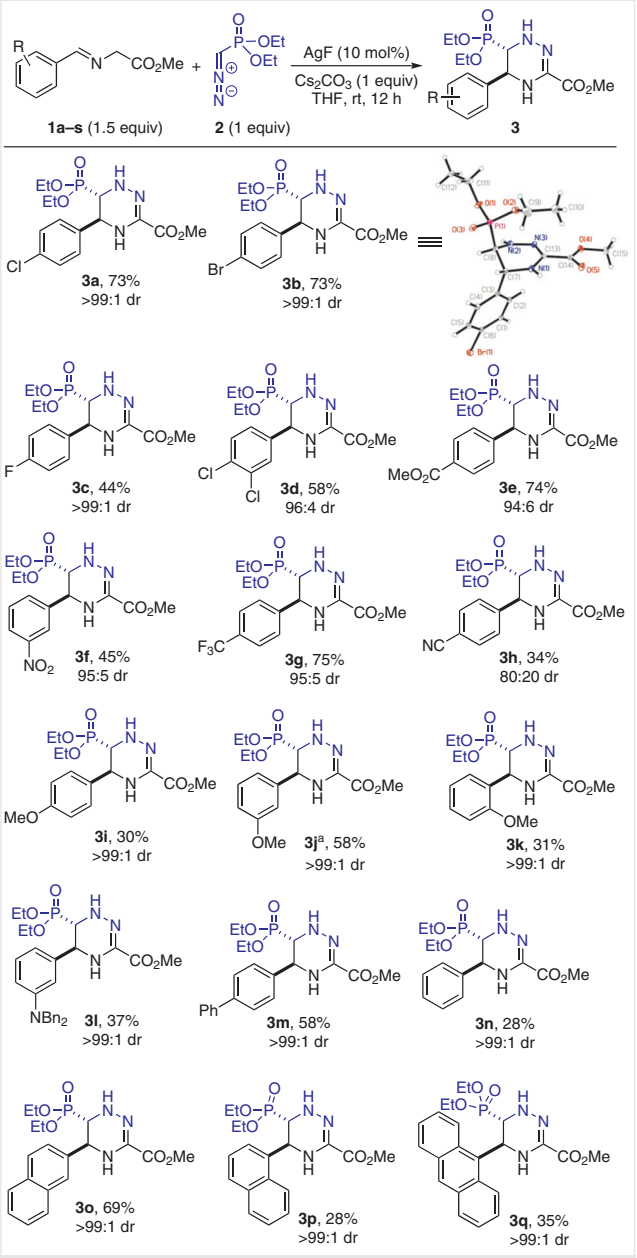
1a (1.5 equiv) **2** (1 equiv) **3a**

Entry	Catalyst	Base (equiv)	Solvent	Yield[b] (%)	dr[c]
1	none	DBU (0.5)	THF	22	>99:1
2	$AgNO_3$	Cs_2CO_3 (1)	THF	56	>99:1
3	$AgNO_3$	K_2CO_3 (1)	THF	0	–
4	$AgNO_3$	Na_2CO_3 (1)	THF	0	–
5[d]	$AgNO_3$	Cs_2CO_3 (1)	THF	0	–
6[e]	$AgNO_3$	Cs_2CO_3 (1)	THF	27	>99:1
7	AgOAc	Cs_2CO_3 (1)	THF	52	>99:1
8	Ag_2O	Cs_2CO_3 (1)	THF	12	>99:1
9	Ag_2CO_3	Cs_2CO_3 (1)	THF	43	>99:1
10	AgCl	Cs_2CO_3 (1)	THF	37	>99:1
11	$AgBF_4$	Cs_2CO_3 (1)	THF	24	>99:1
12	$AgSbF_6$	Cs_2CO_3 (1)	THF	30	>99:1
13	AgF	Cs_2CO_3 (1)	THF	57	>99:1
14	AgF	Cs_2CO_3 (1)	CH_2Cl_2	36	>99:1
15	AgF	Cs_2CO_3 (1)	toluene	42	>99:1
16	AgF	Cs_2CO_3 (1)	1,4-dioxane	38	>99:1
17	AgF	Cs_2CO_3 (1)	NMP	46	>99:1
18	AgF	Cs_2CO_3 (1)	DMF	51	>99:1
19	AgF	Cs_2CO_3 (1)	DMSO	31	>99:1
20[f]	AgF	Cs_2CO_3 (1)	THF	73	>99:1

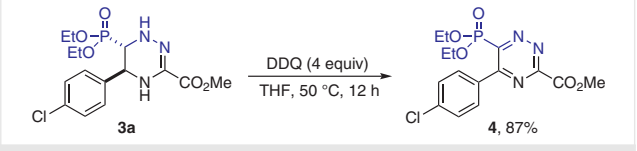
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), Ag catalyst (0.02 mmol), base (0.5–1 equiv), solvent (2 mL), argon atmosphere, 12 h.
[b] Isolated yield.
[c] Determined by ^{31}P NMR spectroscopy of the isolated product; the dr values for the isolated and crude products were identical.
[d] The reaction was performed at 0 °C.
[e] **1a** (1 equiv) and **2** (1.5 equiv) were used.
[f] Reaction conditions: **1** (0.45 mmol), **2** (0.3 mmol), AgF (0.03 mmol), Cs_2CO_3 (0.3 mmol), THF (3 mL), argon atmosphere, 12 h.

6-trifluoromethyl group significantly attracts electron density from the N^2 atom of the triazine ring, such that this atom does not have sufficient electron density and prefers to be sp^3 hybridized to retain sufficient electron density. On the other hand, the 6-ester and 6-phosphoryl groups are less electron-withdrawing, so that the N^2 atoms of the triazine rings are sufficiently electron-rich to permit the formation of C=N double bonds.

The synthetic utility of our reaction was demonstrated by the dehydrogenation of the tetrahydro-1,2,4-triazine product **3a** to give the phosphorylated triazinecarboxylate ester **4** (Scheme 3). This transformation might serve as an alternative means for preparing a novel class of phosphorylated triazines and their derivatives.

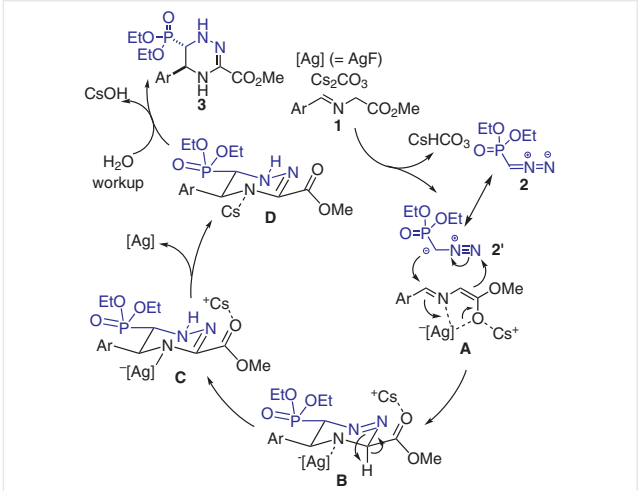


Scheme 2 Substrate scope of the [3+3] annulation of glycine imino esters with Seyferth–Gilbert reagent. *Reagents and conditions*: **1** (0.45 mmol), **2** (0.3 mmol), AgF (0.03 mmol), Cs_2CO_3 (0.3 mmol), THF (3 mL), argon atmosphere, 12 h. The dr was determined by ^{31}P NMR spectroscopy of the isolated product. [a] **1j** (2 equiv) was used.



Scheme 3 Transformation of **3a** into the triazine derivative **4**

Based on previous analogous studies,[12c] a mechanism for Ag-catalyzed [3+3] annulation of glycine imino esters with Seyferth–Gilbert reagent is proposed (Scheme 4). In the presence of Cs_2CO_3 and the AgF catalyst, the glycine imino ester **1** is deprotonated to form a Ag/Cs-coordinated enolate complex **A**. Meanwhile, the Seyferth–Gilbert reagent **2** tautomerizes to form **2′**, which then undergoes [3+3] annulation with **A** to form an Ag/Cs-amide intermediate **B**. The less sterically hindered *trans*-configuration of the aryl and phosphoryl groups probably results in a favorable chair-form conformation of intermediate **B**. Subsequently, intermediate **B** tautomerizes to give a more stable species **C** through conjugation of the imino group with the ester group. Upon elimination of Ag salt for a subsequent catalytic cycle, the resulting Cs–amide species **D** is formed. During aqueous workup, the species **D** is protonated by water to give the desired phosphorylated tetrahydro-1,2,4-triazine-carboxylate ester product **3**.



Scheme 4 Proposed mechanism

In conclusion, we have developed a Ag-catalyzed [3+3] annulation of glycine imino esters with Seyferth–Gilbert reagent.[17] A variety of novel phosphorylated tetrahydro-1,2,4-triazinecarboxylate esters were synthesized with exceptional diastereoselectivities. The products can further undergo dehydrogenation to give the triazinecarboxylate esters. Diversifications of the tetrahydrotriazinecarboxylate esters to other functionalized analogues and a study of their biological activities are our future objectives, based on this work.

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Supporting Information

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Primary Data

for this article are available online at https://doi.org/10.1055/s-0039-1690894 and can be cited using the following DOI: 10.4125/pd0116th.

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(16) CCDC 1977600 contains the supplementary crystallographic data for compound **3b**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(17) **Methyl 5-(4-Aryl)-6-(diethoxyphosphoryl)-1,4,5,6-tetrahydro-1,2,4-triazine-3-carboxylates 3a–q; General Procedure**

An oven-dried 10 mL Schlenk tube equipped with a stirring bar and capped with a rubber septum was charged with the appropriate glycine imino ester **1** (1.5 equiv, 0.45 mmol), AgF (0.03 mmol, 10 mol %), and Cs_2CO_3 (1 equiv, 0.30 mmol). The tube was evacuated and backfilled with argon three times. THF (1.5 mL) was transferred into the tube under a positive argon pressure by using a syringe. A solution of Seyferth–Gilbert reagent **2** (1 equiv, 0.3 mmol) in THF (1.5 mL) was then transferred into the mixture by syringe under a positive argon pressure, and the mixture was stirred under argon at rt for 12 h. The mixture was finally concentrated in vacuo in a rotary evaporator and the residue was purified by flash chromatography [silica gel, PE–

EtOAc then EtOAc–MeOH (20:1)].

Methyl 5-(4-Chlorophenyl)-6-(diethoxyphosphoryl)-1,4,5,6-tetrahydro-1,2,4-triazine-3-carboxylate (3a)

Brown solid; yield: 85.6 mg (73%); mp 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.29 (m, 2 H), 7.25–7.21 (m, 2 H), 5.73 (s, 1 H), 5.56 (t, *J* = 2.2 Hz, 1 H), 4.78–4.83 (m, 1 H), 4.11–3.90 (m, 4 H), 3.86 (s, 3 H), 3.21–3.17 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.08 (p, *J* = 8.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.1, 138.7 (d, *J* = 4.5 Hz), 136.2, 134.5, 129.0, 128.8, 63.0 (d, *J* = 6.7 Hz), 62.7 (d, *J* = 7.0 Hz), 54.2, 53.1, 52.9 (d, *J* = 154.1 Hz), 16.5 (d, *J* = 5.9 Hz), 16.3 (d, *J* = 6.1 Hz). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}ClN_3O_5P$: 390.0980; found: 390.0981.