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A convenient synthesis of new phosphonomethyl-containing 4,5-dihydropyridazin-3(2*H*)-ones

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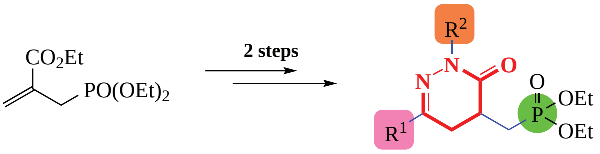
An expedient access to novel 4-phosphonomethyl-containing 2,6-disubstituted 4,5-dihydropyridazin-3(2*H*)-ones involves the reaction of β-phosphono γ′-keto ester intermediates with hydrazines. The construction of the pyridazinone ring allows the installation of various substituents at the positions 2 and 6 as well as a valuable 4-positioned phosphonomethyl fragment.



10 examples
76–88% yields

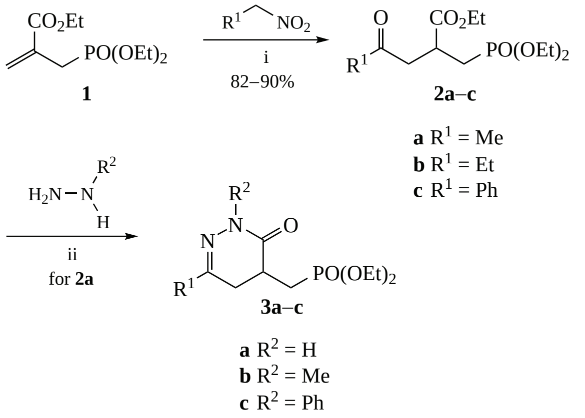
Keywords: pyridazin-3(2*H*)-ones, phosphonates, nitroalkanes, γ-keto ester, Michael addition, Nef reaction.

Pyridazin-3(2*H*)-ones and their 4,5-dihydro analogues are valuable scaffolds in druggable synthetic molecular architectures, attracting considerable and lasting attention from organic and medicinal chemists.[1] 4,5-Dihydropyridazin-3(2*H*)-one motif is present in compounds that exhibit anti-tubercular[2] and antibacterial activities[3] as well as enzyme inhibitors, including Siguazodan, a selective phosphodiesterase inhibitor,[4] and 6-vinyl-4,5-dihydropyridazin-3(2*H*)-one derivatives being a highly potent COX-2 inhibitors.[5] Several pharmaceutically active compounds, such as Indolidan, Pimobendan and Levosimendan, actively used to treat heart failure, contain the 4,5-dihydropyridazin-3(2*H*)-one core.[6] The selective installation of various substituents on the 4,5-dihydropyridazin-3(2*H*)-one backbone, leading to broad substitution patterns, represents a current challenge for the modulation of biological properties.[7,8] Although several methods allow the preparation of functionalized 4,5-dihydropyridazin-3(2*H*)-ones,[9] the installation of phosphonate groups is scarce. Among the most relevant examples are 4-diethoxyphosphoryl-4,5-dihydropyridazin-3(2*H*)-one derivatives described by Albrecht *et al.*[10]

To our knowledge, the synthesis of 4,5-dihydropyridazin-3(2*H*)-ones bearing a 4-positioned phosphonomethyl group, which could contribute to extending the molecular diversity within this heterocycle family, remains a challenge. As part of a research program devoted to synthesizing phosphono azaheterocyclic compounds,[11] we herein describe a new approach towards 4-phosphonomethyl-containing 2,6-disubstituted-4,5-dihydropyridazin-3(2*H*)-one derivatives. Our methodology involves a two-step sequence for constructing one C–C and one C–N bond.

The key phosphonomethyl-containing γ-keto esters were obtained using a one-pot method adapted from the report by Ballini *et al.*[12] Indeed, conjugate addition of 1-nitroethane to allylphosphonate **1** in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) allows the preparation of γ-keto ester **2a** (90% yield) through the Michael addition–Nef conversion sequence (Scheme 1). This strategy can be also extended to propyl and benzyl nitro derivatives to obtain the corresponding phosphonomethyl-substituted γ-keto esters **2a–c** in high yields.

We next examined the transformation of γ-keto esters **2a–c** into phosphonomethyl 4,5-dihydropyridazin-3(2*H*)-ones. We began our study by using γ-keto ester **2a** as the model in reaction with hydrazine derivatives. No conversion of compound **2a** was observed in EtOH at room temperature even after 48 h (Table 1, entry 1). Refluxing in ethanol proved necessary for the formation of 4,5-dihydropyridazin-3(2*H*)-one **3a** in 88% yield (entry 2). Gratifyingly, addition of a catalytic (5 mol%) amount of acetic acid allowed completion of the cyclization in shorter reaction time (5 h instead of 8 h) to give pyridazinone **3a** in good yield (entry 3). A further improvement was achieved using toluene and AcOH (5 mol%). Indeed, the reaction course could be shortened to 3 h (entry 4). Finally, the combination toluene–AcOH was revealed to be the most suitable one for the reaction of methyl- and phenylhydrazines with keto ester **2a** (entries 5 and 6) to



Scheme 1 *Reagents and conditions*: i, DBU, MeCN, room temperature, 16 h, then 60 °C, 16 h; ii, for conditions and yields, see Table 1.

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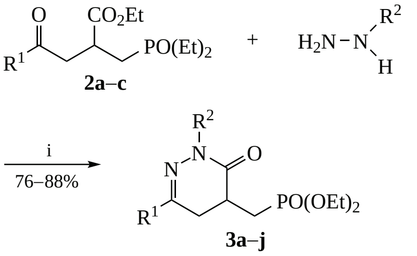
Table 1 Preparation of 4,5-dihydropyridazin-3-ones **3a**–**c** from keto ester **2a.**

Entry	Hydrazine	Conditions	t/h	Product	Yield (%)
1	H_2NNH_2	EtOH, ~ 25 °C	48	–	–
2	H_2NNH_2	EtOH, reflux	8	**3a**	88
3	H_2NNH_2	EtOH, AcOH[a], reflux	5	**3a**	86
4	H_2NNH_2	PhMe, AcOH[a], reflux	3	**3a**	88
5	H_2NNHMe	PhMe, AcOH[a], reflux	3	**3b**	86
6	H_2NNHPh	PhMe, AcOH[a], reflux	3	**3c**	81

[a] 5 mol% to reactant **2a**.



3a R^1 = Me, R^2 = H
3b R^1 = R^2 = Me
3c R^1 = Me, R^2 = Ph
3d R^1 = Et, R^2 = H
3e R^1 = Et, R^2 = Me
3f R^1 = Et, R^2 = Ph
3g R^1 = Ph, R^2 = H
3h R^1 = R^2 = Ph
3i R^1 = Et, R^2 = $(CH_2)_2OH$
3j R^1 = Et, R^2 = $(CH_2)_2CN$

Scheme 2 *Reagents and conditions*: i, AcOH (5 mol%), toluene, reflux, 3 h.

afford pyridazinones **3b**,**c** in 86 and 81% yields, respectively. It is worthy to note that large excess of hydrazine, a condition often used in such condensation, was not required, and the use of 1.2 equiv. of hydrazines was more than sufficient.

Keto esters **2a–c** were then reacted with some other hydrazine derivatives under the optimized reaction conditions to afford a new family of 4-phosphonomethyl-4,5-dihydropyridazin-3-ones **3a–j** in good yields (Scheme 2).

Although 2-hydroxy- and 2-cyanoethylhydrazines formed 4,5-dihydropyridazin-3-ones **3i**,**j** in good yields, other functionalized hydrazine derivatives such as 4-nitrophenyl- or 3,5-dichlorophenylhydrazines did not furnish the expected products with keto esters **2a**,**b**. In these cases, several by-products were formed, including acyclic hydrazones through partial degradation during purification. We also noticed that under these reaction conditions, hydrazide derivatives such as 2-phenylaceto or benzenesulfono hydrazides did not form the expected 4,5-dihydropyridazin-3-ones. These findings may be explained by the effect of the electron-deficient substituent which reduces the nucleophilicity of the neighbouring nitrogen atom preventing the cyclization process.

NMR and HRMS data are consistent with the obtained product structures. $^{31}P\{1H\}$–NMR spectra show a single signal around 29.29–29.90 ppm indicating that the products are pure. ^{13}C NMR spectra contained doublets around 23.05–27.35 ppm showing the coupling between phosphorus and carbon in α-position with a coupling constant $^1J_{C-P}$ = 143.2–159.7 Hz. Due to the coupling of non-equivalent protons both with each other and with phosphorus, the ^1H NMR spectrum appears complicated.

In summary, we have described a synthetic approach to the preparation of a novel family of phosphonomethyl-containing 2,6-disubstituted-4,5-dihydropyridazin-3(2*H*)-ones. The synthetic method was based on the preparation of γ-keto ester intermediates from nitroalkanes and allylphosphonate precursors. Construction of the 4,5-dihydropyridazin-3(2*H*)-one ring was achieved using various hydrazines. Optimized conditions, using toluene as the solvent and AcOH (5%) as an additive, provided the application of nearly equivalent amounts of hydrazines. Studying the reactivity and evaluating the biological activity of the synthesized 4,5-dihydropyridazin-3(2*H*)-ones will be the subject of ongoing studies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.016.

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