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Diethoxyphosphinyl acetic acid hydrazide: a uniquely versatile reagent for the preparation of fused [5,5]-, [5,6]-, and [5,7]-3-[(*E*)-2-(arylvinyl)]-1,2,4-triazoles

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Abstract—Diethoxyphosphinyl acetic acid hydrazide is a unique reagent that provides a convenient and efficient process to prepare fused [5,5]-, [5,6]-, and [5,7]-3-[(*E*)-2-(arylvinyl)]-1,2,4-triazoles from aldehydes and alkoxyimines. The process involves three steps without isolation of any intermediates to afford 1,2,4-triazoles in modest to excellent overall yield.

Fused 1,2,4-triazoles represent an interesting class of compounds due to their versatile biological activity and their synthesis has attracted the attention of several synthetic groups.[1] The most common synthetic route to 1,2,4-triazoles involves the condensation of an alkoxyimine with an acyl hydrazide to give an intermediate amidrazone that then cyclodehydrates to yield a 1,2,4-triazole (Scheme 1).[2]

We required a versatile synthesis of fused-[(*E*)-2-(arylvinyl)]-1,2,4-triazoles (Scheme 1), $n = 2$, 3, 4; $R_2 = [(E)$-2-(arylvinyl)], in which an α,β-unsaturated hydrazide was considered as a possible starting material.[3] However, syntheses of α,β-unsaturated hydrazides from alcohol, aldehyde, acid, or ester precursors are often a multi-step process and can be problematic and tedious.[4] This prompted us to search for a new, straightforward synthetic method for the triazole ring system that would avoid the preparation of the problematic α,β-unsaturated hydrazide.

Retrosynthetically, the target compounds could be constructed from three precursors: an aldehyde, an alkoxyimine **2**, and diethoxyphosphinyl acetic acid hydrazide **1**, which is readily prepared in excellent yield by modification of the literature method.[5,6] Thus, condensation of a cyclic alkoxyimine **2** with **1** followed by Horner–Emmons reaction[7] of the resulting phosphonate with an aromatic or heterocyclic aldehyde and subsequent cyclodehydration should provide the fused 3-[(*E*)-2-(arylvinyl)]-1,2,4-triazoles (Scheme 2).

We began our model study with the commercially available seven-membered ring alkoxy imine, 3,4,5,6-tetrahydro-7-methoxy-2*H*-azepine **2a**. Condensation of **2a** with **1** in methylene chloride at room temperature provided, after concentration, the crude amidrazone **3** as a yellow oil. Subsequently, the Horner–Emmons reaction was carried out with benzaldehyde in EtOH at room temperature using NaOEt as the base to give 3-phenyl-*N*′-(4,5,6,7-tetrahydro-3*H*-azepin-2-yl)acrylic acid hydrazide **4** as a yellow oil. The ^{1}H NMR spectra showed a purity of >95% for each of the intermediates **3** and **4**. Cyclodehydration of **4** was accomplished in refluxing toluene with a catalytic amount of HOAc to afford *trans*-3-styryl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepine **5a** in 36% overall yield from **1** (Scheme 3).

The successful synthesis of **5a** in a stepwise manner, prompted us to explore a more convenient and efficient construction of the 1,2,4-triazole system by combining all three reactions in a single operation. We found that the synthesis was readily achieved in one pot using toluene as the solvent. In the event, the alkoxyimine reacts with **1** in toluene at room temperature after which a 21%

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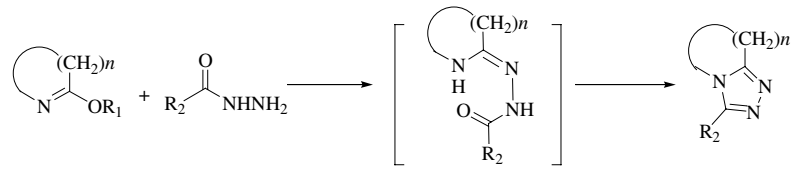
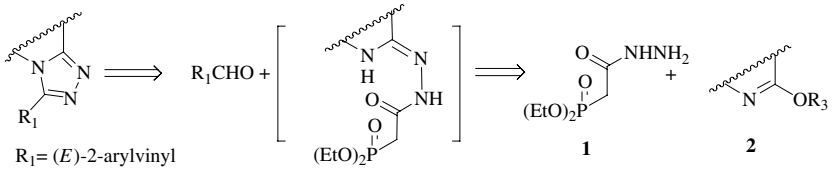
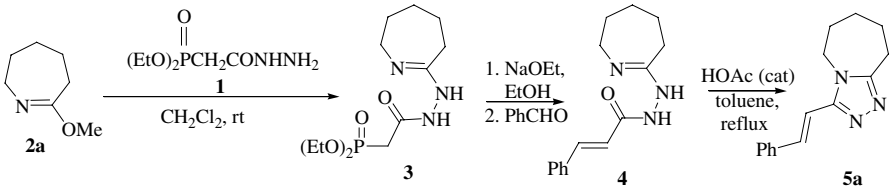


Scheme 1.



Scheme 2.

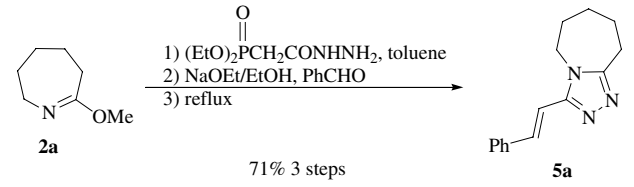


Scheme 3.

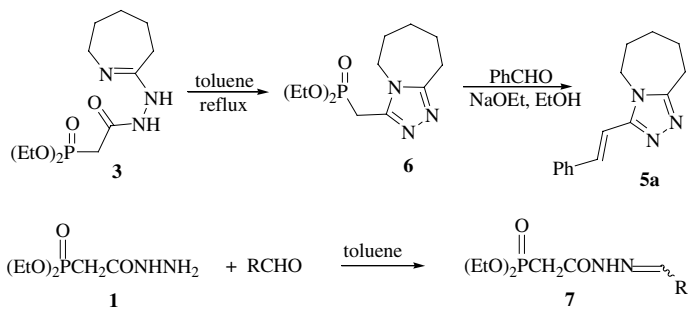
solution of NaOEt in EtOH is added followed by the addition of the aldehyde. The reaction mixture is heated at reflux for several hours and, after workup, it produces the fused triazole **5a** in 71% yield (Scheme 4).

We found that the order of addition of reagents is critical to the success of the reaction. If **1** is added to **2**, in the absence of base or aldehyde, the initial product **3** cyclizes cleanly to the 3-(triazol-5-yl)methyl phosphonate **6**. Subsequent addition of NaOEt and the aldehyde affords the expected vinyl triazole, for example, **5a** although there can be some variability in yield. However, when **1**, the aldehyde and NaOEt are added to the alkoxyimine, we observe rapid reaction of the aldehyde with **1** and formation of the stable acyl hydrazone **7** (stereochemistry not determined; Scheme 5).

Encouraged by these results, we explored the scope and generality of this methodology. As shown in Table 1, this is a general method to prepare fused [5,6]- and fused [5,7]-3-[(*E*)-2-(arylvinyl)-1,2,4-triazoles and is compatible with aryl groups containing electron donating groups or electron withdrawing groups as well as five- and six-membered ring heterocycles. The workup is straightforward and involves simple concentration of the toluene solution and addition of water to the residue to precipitate the desired product in high chemical purity. It is noteworthy that there was no evidence for the (*Z*)-regioisomer in the ^{1}H NMR spectrum of the isolated products. The simplicity of this purification

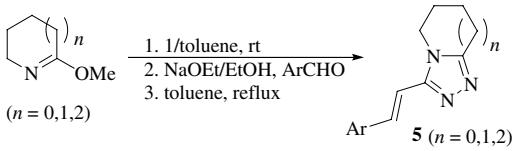


Scheme 4.



Scheme 5.

Table 1. Synthesis of fused 1,2,4-triazoles using diethoxyphosphinylacetic acid hydrazide



Entry	*n*	ArCHO	Product[a]	Ar	Yield (%)
1	2	Benzaldehyde	**5a**	Ph	71
2	2	Thiazole-2-carboxaldehyde	**5b**	Thiazol-2-yl	66
3	2	4-Methoxybenzaldehyde	**5c**	4-MeO-Ph	72
4	2	4-Cyanobenzaldehyde	**5d**	4-NC-Ph	72
5	1	Benzaldehyde	**5e**	Ph	77
6	1	4-Chlorobenzaldehyde	**5f**	4-Cl-Ph	81
7	1	4-Methoxybenzaldehyde	**5g**	4-MeO-Ph	75
8	1	Pyridine-2-carboxaldehyde	**5h**	Pyrid-2-yl	69
9	1	Thiophene-2-carboxaldehyde	**5i**	Thien-2-yl	57
10	0	Benzaldehyde	**5j**	Ph	37[b]
11	0	4-Chlorobenzaldehyde	**5k**	4-Cl-Ph	33[c]

[a] The ^{1}H NMR spectra for all products showed the presence of only the (*E*)-regioisomer.
[b] 48 h reflux in HOAc to complete the triazole ring closure.
[c] 72 h reflux in HOAc to complete the triazole ring closure.

procedure further enhances the suitability of the overall process for large-scale synthesis. The synthesis of **5a** in an overall yield of 71% (Scheme 5, Table 1, entry 1) is a representative example that illustrates the effectiveness of this one-pot process.[8,9]

However, we did encounter a limitation when we used the one-pot approach to prepare fused [5,5]-3-(2-arylvinyl)-1,2,4-triazoles. In this case there was no evidence for the desired product even after prolonged heating (up to 72 h) in toluene. However, if the precursor acrylic acid analogue is isolated it could be cyclized, albeit in modest yield (Table 1, entries 10 and 11), by prolonged heating in acetic acid (2–3 days) to generate the desired fused [5,5]-3-[(*E*)-2-(arylvinyl)]-1,2,4-triazole.[10] Presumably, the modest yields reflect the known difficulty of constructing such fused [5,5]-1,2,4-triazoles due to ring strain.[11]

In summary, we have developed a general method to prepare fused [5,6]-, and [5,7]-3-[(*E*)-2-(arylvinyl)]-1,2,4-triazoles using diethoxyphosphinyl acetic acid hydrazide. This one-pot reaction proceeds in good to excellent yield and produces only the (*E*)-regioisomer. Modest yields are obtained for the fused [5,5]-3-[(*E*)-2-(arylvinyl)]-1,2,4-triazoles using modified cyclization conditions. Further work with aliphatic aldehydes, ketones, and conjugated systems is in progress and will be reported in due course.

Acknowledgements

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8. Experimental procedure for the preparation of 3-styryl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyridine, **5e**. Diethoxyphosphinyl acetic acid hydrazide (1.05 g, 5.0 mmol) was added to a toluene (15 mL) solution of 2,3,4,5-tetrahydro-6-methoxypyridine, (0.57 g, 5.0 mmol) under N_2 to afford a cloudy suspension. After stirring overnight

at ambient temperature, the resulting clear solution was treated with NaOEt solution (21 wt % in EtOH, 2.05 mL, 5.5 mmol) followed by benzaldehyde (0.51 mL, 5.0 mmol). The reaction mixture was heated at reflux for 2 h and then concentrated to a yellow solid residue. Water (30 mL) was added to this residue and the resulting yellow slurry was stirred for 20 min. The slurry was filtered and the solid product was washed with water and dried to afford **5e** as a light yellow solid (0.88 g, 77%). Mp: 161–163 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, $J = 16$ Hz, 1H), 7.53 (d, $J = 7$ Hz, 2H), 7.39 (m, 3H), 6.84 (d, $J = 16$ Hz, 1H), 4.01 (t, $J = 6$ Hz, 2H), 3.03 (t, $J = 6$ Hz, 2H), 2.07 (m, 2H), 1.96 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 151.3, 151.2, 135.8, 134.8, 128.9, 128.8 (2C), 126.9 (2C), 110.7, 42.6, 22.5, 22.4, 19.8. Anal. Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.53; H, 6.69; N, 18.85.

9. All compounds were completely characterized and gave satisfactory elemental analyses (±0.4%) or HRMS, ^{1}H, ^{13}C and mass spectra.
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