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Aza-Michael addition of 1,2-diazoles to structurally diverse enones: Efficient methods toward β-amino ketones

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Abstract

An efficient and mild protocol was realized using 1,2-diazoles and related heterocycles with cyclic and acyclic enones in presence of T3P (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide) toward the regioselective formation of *N*-cycloalkyl heterocycles at room temperature. The developed reaction conditions showcased good selectivity over a wide range of 1,2-diazoles and enones by delivering *N*-cycloalkyl heterocycles in excellent yields.

KEYWORDS

1,2-diazoles, aza-Michael addition, cyclic enones, *N*-cycloalkyl heterocycles, T3P-mediated

1 | INTRODUCTION

Synthesis of *N*-cycloalkyl heterocyclic motifs has gained utmost significance in recent years on account of their significance in pharmaceutical and biological sciences.[1]

The recognition of azole motifs in most of the current drugs and advanced drug candidates further increases their significance in medicinal chemistry (Figure 1). However, aza-Michael addition approach is a standout protocol among the most essential and powerful route for C-N bond formation; nevertheless addition of azoles to cyclic enones is quite troublesome because of less nucleophilic nature of the azoles and due to the structural complexity of the cyclic enones.[2] It is evident from the literature reports that metals,[3] lanthanides,[4] inorganic strong supports,[5] fluorides,[6] organocatalysts,[7] bases,[8] and even enzymes[9] were utilized toward the successful accomplishment of aza-Michael addition reactions. In recent times, catalyst-free aza-Michael addition reactions have also been explored using azoles and β,γ-unsaturated-α-keto esters/electron deficient olefins.[10] Regardless of colossal advancement in this field, the addition of azoles to cyclic enones has been rarely investigated.[2a,5b,11]

Despite the fact that the Michael addition of azoles to cyclic enones is conducted at high pressure[11g] and solvent-free Brønsted acid-catalyzed reaction conditions,[11h] these strategies utilize harsh reaction conditions and mostly examined for straightforward unsubstituted azoles (Scheme 1). Likewise with un-

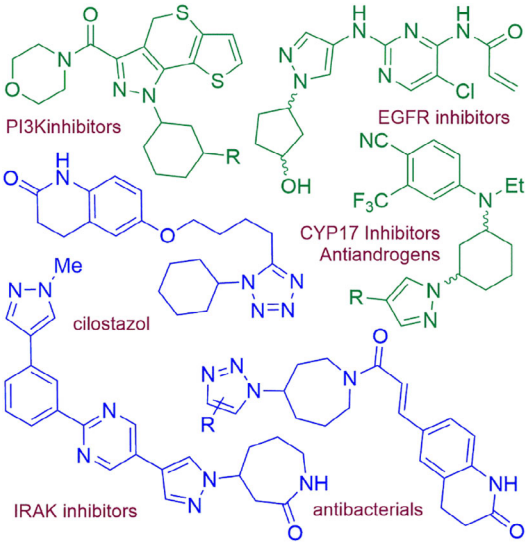
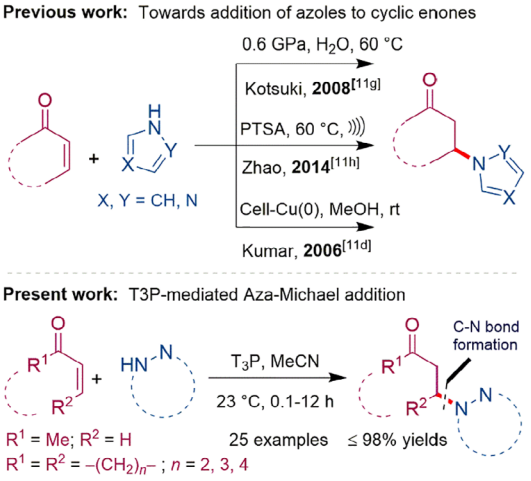


FIGURE 1 Advanced drug candidates and drugs containing *N*-cycloalkyl azoles [Colour figure can be viewed at wileyonlinelibrary.com]



SCHEME 1 Approaches toward addition of azoles to cyclic enones [Colour figure can be viewed at wileyonlinelibrary.com]

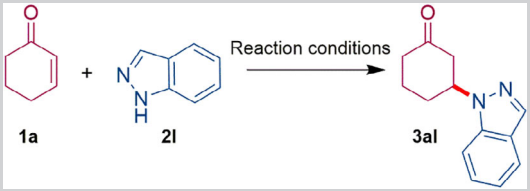
symmetrical azoles; the formation of high level of positional isomers is self-evident. In our efforts to envisage simple and metal free conditions for the addition of azoles to cyclic enones, we have developed a new method using stoichiometric T3P as reagent for aza-Michael addition of azoles to cyclic enones at room temperature. The advantage of using T3P as a choice of reagent over previously reported methods being its robustness and ease of handing to accomplish C-N bond formation via Aza-Michael addition phenomenon.

With an intention of establishing an operationally simple and robust method for the addition of azoles to cyclic enones, we have taken cyclohex-2-en-1-one (**1a**) and indazole (**2l**) as model substrates. We have carried out the reaction of cyclohex-2-en-1-one (**1a**) and indazole (**2l**) using T3P (50% wt/vol in EtOAc, 2 equiv.) at 23°C for 12 hours.

The reaction conditions have offered the corresponding product **3al** in 60% yield, along with the unreacted starting materials (Table 1, Entry 1). Encouraged by these results, we then decided to optimize the reaction conditions by considering the effects of different solvents and temperatures (Entries 2–7). It was examined that the use of polar protic solvent MeOH (Entry 2) gave unsatisfactory result, while the usage of non-polar solvents considerably improved the yield of the desired product (Entries 3–5). On the other hand, employing polar aprotic solvents such as DMF and MeCN (Entry 6–7) resulted in significant improvement in the yields as the highest yield of 97% was obtained by using acetonitrile as solvent (Entry 7). Next, to scrutinize the importance of T3P, control reactions between **1a** and **2l** were performed in the absence of T3P at different reaction temperatures and time (Entries 8–10). It was evident from the obtained results that, under T3P-free reaction conditions the progress of the reaction was inhibited. Further, the reaction parameters were optimized by utilizing different amounts of reagents at different reaction temperature and time (Entries 11–16). On the basis of these experiments, higher and very slight excess equivalents of azoles and T3P were observed to be productive for this transformation (Entries 11–13). However, lowering the amount of T3P was found not appropriate for the progress of the reaction which is exemplified by the lower yields of the desired products (Entries 14–15). Next, performing the reaction at 80°C (Entry 16) leading to the formation of multiple by-products and only 30% of the desired product could be isolated. Upon extensive screening of the reaction conditions, it was discerned that the reaction of 1.0 mmol of **1a** with 1.0 mmol of **2l** in the presence of 1.1 equiv. of T3P in acetonitrile solvent at 23°C for 2 hours to achieve the maximum yield of the product **3al** in 98% (Table 1, Entry 13).

With these reaction conditions in hand, we investigated the scope of the reaction with different azoles **2a**-**p** and the results are summarized in Scheme 2. The Michael addition of pyrazoles **2a**-**f** proceeded smoothly with excellent yields of product **3aa**-**af**, with an exception to 4-nitro-1*H*-pyrazole (**2d**) where 65% of the product was obtained. The Michael addition of 1,2,3-triazole **2g** and tetrazole **2j** without substitution resulted in two regioisomers, but 1,2,4-triazoles **2h**-**i** delivered only one regioisomer. In continuation, the substituted tetrazole **2k** and indazoles **2m**-**o** with substitution and without substitution participated well toward the completion of the reactions with high yields and regioselectivity. Next, the aza-Michael addition reaction of benzotriazole (**2p**) resulted in two regioisomers **3ap** and **3ap′** in the ratio

TABLE 1 Optimization of reaction conditions for the reaction of **1a** with **2l**[a] [Colour table can be viewed at wileyonlinelibrary.com]



Entry	Reagents (Equiv.)	Reaction conditions	% Yield 3al[b]
1	T3P (1.5)	EtOAc, 23°C, 12 h	60
2	T3P (1.5)	MeOH, 23°C, 12 h	30
3	T3P (1.5)	Et_2O, 23°C, 12 h	65
4	T3P (1.5)	Dioxane, 23°C, 12 h	67
5	T3P (1.5)	CH_2Cl_2, 23°C, 12 h	90
6	T3P (1.5)	DMF, 23°C, 12 h	50
7	T3P (1.5)	MeCN, 23°C, 12 h	97
8	-	MeCN, 80°C, 12 h	0
9	-	MeCN, 23°C, 1 h	0[c]
10	-	MeCN, 23°C, 24 h	0
11	T3P (2)	MeCN, 23°C, 12 h	97
12	T3P (1.3)	MeCN, 23°C, 4 h	98[d]
13	**T3P (1.1)**	**MeCN, 23°C, 2 h**	**98[e]**
14	T3P (0.5)	MeCN, 23°C, 12 h	40[e]
15	T3P (0.2)	MeCN, 23°C, 12 h	10[e]
16	T3P (1.1)	MeCN, 80°C, 1 h	30[e]

[a]Unless otherwise indicated: All reactions were performed using 1.0 mmol **1a** and 2.0 mmol **2l** in 2 mL of solvent.
[b]Isolated yields.
[c]Reaction was carried out in microwave reactor.
[d]Reaction was carried out with 1.3 mmol **2l**.
[e]Reaction was carried out with 1.0 mmol **2l**.

(8.5:1.5). At last, to our dismay, no addition product **3aq** was observed with imidazole (**2q**), where only starting enone compound could be recovered.

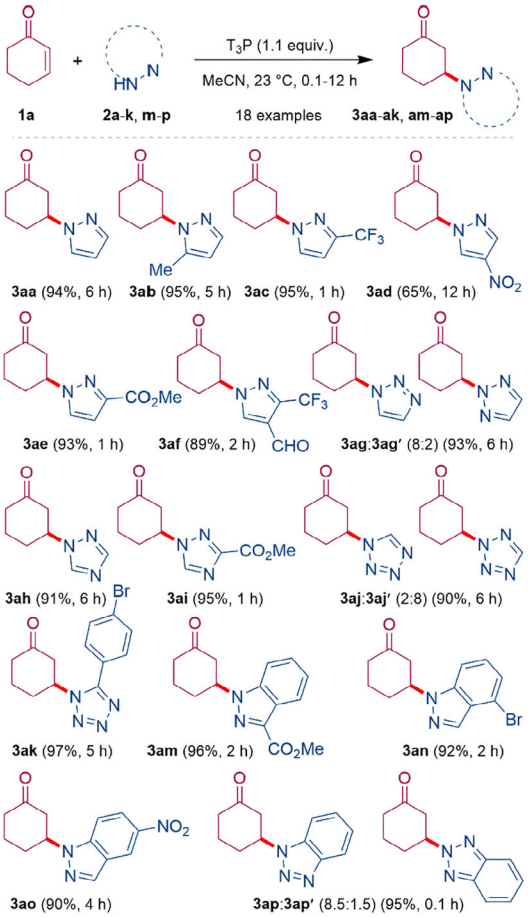
Then, we have extended the application of developed reaction conditions to different enones **1b-d** with azole **2a**, **l**, **m** and we were greeted with excellent yields of aza-Michael addition products **3ba**, **bl**, **ca**, **cl**, **cm**, **dl** with higher regioselectivity (Scheme 3).

After demonstrating considerable substrate scope for the developed reaction conditions, we forged ahead to propose a plausible reaction mechanism for this chemical transformation (Scheme 4). According to the proposed mechanism,[12] the nucleophilic attack of oxygen atom of enone **1a** on to the phosphorus-atom of T3P (**A**) leading to the formation of intermediate **B** which may form the corresponding resonance structure **B′**. Next, the nucleophilic addition of azole **2** on to in situ generated carbocation of enone delivers the intermediate **C**, which on subsequent hydrolysis and tautomerization provides the desired product **3**.

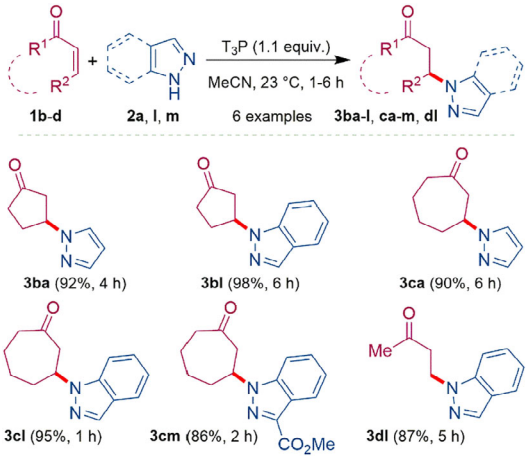
In summary, an efficient and regioselective aza-Michael addition of 1,2-diazoles with cyclic and acyclic enones was realized by employing T3P-mediated reaction conditions. The developed protocol gives an easy entry to rarely explored *N*-cycloalkyl heterocyclic motifs. The described approach revealed excellent selectivity and functional group tolerance by delivering the desired products up to 98% yields.

2 | EXPERIMENTAL SECTION

A 10 mL round bottom flask was charged with enones **1a-d** (1.0 mmol), azoles **2a-p** (1.0 mmol) in MeCN (2 mL), then added T3P (1.1 mmol) and the reaction mixture was stirred at room temperature (23°C) for 0.1–-12 hours. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 8:2 and LC–MS), the recation mixture was quenched with saturated

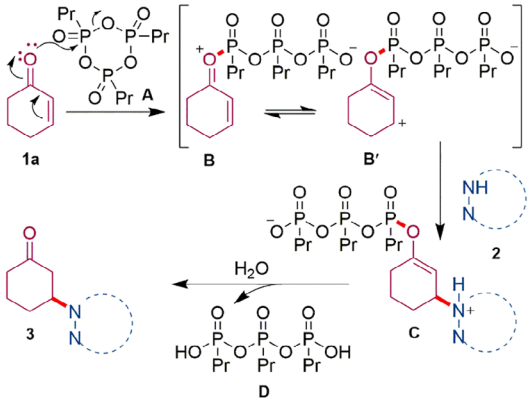


SCHEME 2 Scope of different azoles toward aza-Michael addition [Colour figure can be viewed at wileyonlinelibrary.com]



SCHEME 3 Scope of different enones toward aza-Michael addition [Colour figure can be viewed at wileyonlinelibrary.com]

$NaHCO_3$ solution, diluted with water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified over CombiFlash MPLC using Hexane/EtOAc = 80:20 as an eluent to obtain the desired Aza-Michael addition products **3aa-ap** and **3ba, bl, ca, cl, cm, dl** in high yields.



SCHEME 4 Proposed mechanism of T3P-mediated diazole addition to enones [Colour figure can be viewed at wileyonlinelibrary.com]

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DATA AVAILABILITY STATEMENT

Data available on request from the authors: The data that support the findings of this study are available from the corresponding author upon reasonable request

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