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IODOBENZENE CATALYZED EFFICIENT SYNTHESIS OF FUSED TRIAZOLOPYRIMIDINES USING *m*-CHLOROPERBENZOIC ACID

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Abstract
The oxidative cyclization of 2,6-dimethyl-4-pyrimidinylhydrazones (**2**) and 4,6-dimethyl-2-pyrimidinylhydrazones (**5**) has been accomplished using iodobenzene as a catalyst to furnish fused triazolopyrimidines in the presence of *m*CPBA as a terminal oxidant. The reaction is general, and the target products can be obtained in moderate to good yields.

Keywords: Fused triazolopyrimidine,*m*-chloroperbenzoic acid(*m*CPBA), iodobenzene

Introduction

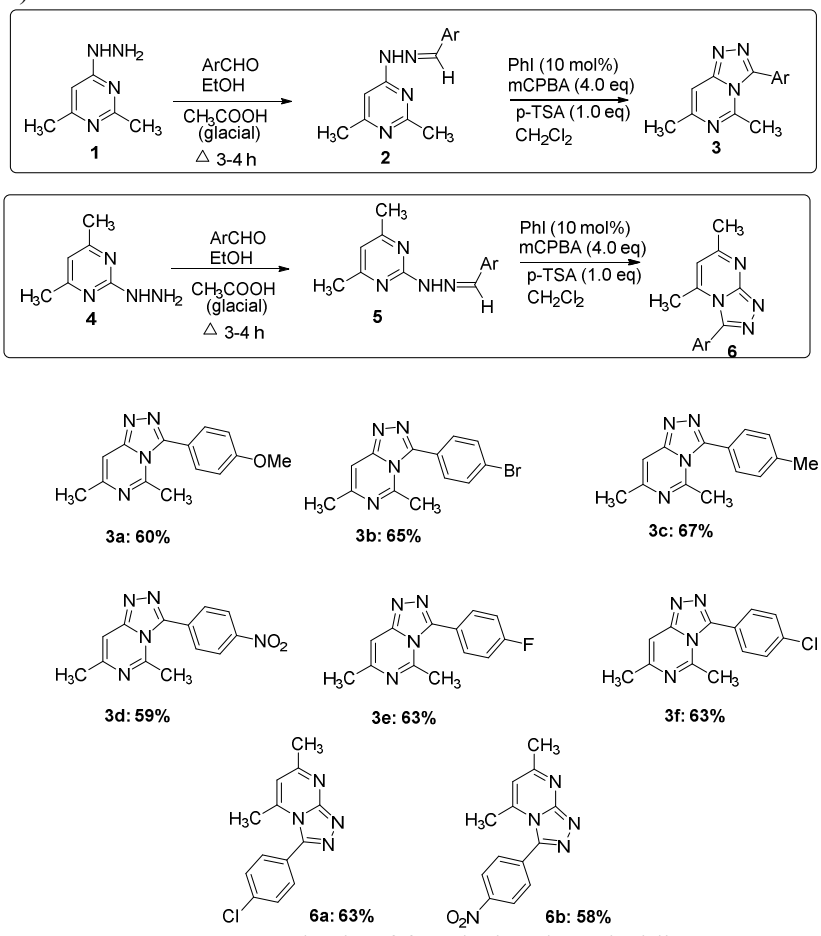
The chemistry of hypervalent iodine organic compounds has experienced impressive developments since the early 1990s. Due to their low toxicity, ready availability, easy handling and reactivity similar to that of heavy metal reagents or anodic oxidation, hypervalent iodine compounds have received a great deal of attention for organic synthesis including asymmetric synthesis [1]. They have been extensively used as mild, highly selective and environmentally friendly reagents in organic reactions, such as oxidations [2], substitutions [3], additions [4] and rearrangement reactions [5].

Fused heterocyclic 1,2,4-triazoles are associated with a number of biological applications.They exhibit properties like CNS depressant[6], antiallergy [7], antimicrobial [8], anti-inflammatory [9], antischistosomal activity [10],anticancer [11]DNA Binding [12] and Photonuclease Activity [13]. In our previous papers, we reported the synthesis of fused 1,2,4-triazolopyrimidines, and 1,2,4-bistriazolopyrimidines using stoichiometric amounts of hypervalent iodine (III) reagent.[14] We report herein the catalytic version of this valuable λ^3-iodane oxidative cyclization in which iodobenzene serves as an excellent organocatlayst. Thus, we developed an efficient iodobenzene catalyzed oxidative protocol for the cyclization of 2/4,6-dimethyl-2-pyrimidinylhydrazones (**2/3**)using *m*CPBA as a terminal oxidant at room temperature.

Results and Discussion

Stoichiometric amounts and often even an excess of the hypervalent iodine reagents have been necessary to achieve the desired transformation. However, several recent publications have shown that it is indeed possible to use only a catalytic amount of an iodine-containing molecule together with a stoichiometric oxidant.[15] The oxidant generates the hypervalent iodine reagent *in situ*, and, after the oxidative transformation, the reduced iodine-containing molecule is re-oxidized. Known oxidants for the preparation of hypervalent iodine compounds from iodine-containing precursors include peracetic acid, sodium perborate, nitric acid, and hydrogen peroxide, *meta*-chloroperbenzoic acid (*m*CPBA). These result paved the way for the development of catalytic reactions with hypervalent iodine compounds. The basic requirement for a successful reaction generating and using hypervalent iodine compounds in only catalytic amounts is the ability of the stoichiometric oxidant to selectively generate the hypervalent iodine compound in the presence of the substrate.

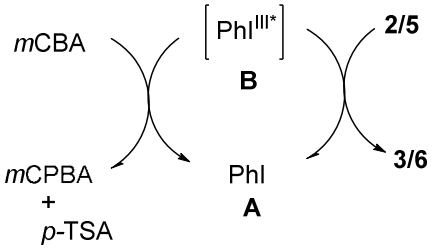
Accordingly, the present study was started by the optimization of oxidative reaction conditions using 1-(4-methoxybenzylidene)-2-(2,6-dimethylpyrimidin-2-yl)hydrazone(**2a**)as a model substrate (**2a**) that can be easily prepared from 4-anisaldehyde and 4-hydrazino-2,6-dimethyl pyrimidine. Treating the substrate **2a**with 10 mol% of iodobenzene (PhI) and 4.0equiv of *meta*-chloroperbenzoic acid (*m*CPBA) at room temperature in dichloromethane (CH_2Cl_2) did not yield the desired fused triazole. However to our delight, addition of *p*-toluenesulphonic acid (*p*-TSA, 1equiv) to the reaction mixture led to the formation of 3-aryl-5, 7-dimethyl-1, 2, 4-triazolo [4,3-c]pyrimidine (**3a**) with 60 % yield at room temperature in 2 hrs (**Scheme 1**).



Scheme 1. Synthesis of fused triazolopyrimidines

Lowering the quantity of *meta*-chloroperbenzoic acid (*m*CPBA) led to decrease in the overall yield of the product formation. The control experiment confirmed that, without iodobenzene, the formation of the desired product was not observed.

With the optimized reaction conditions in hand, the scope of the procedure was studied for the reaction of a series substituted hydrazones (**2b-f**). Reaction proceeded with ease in each case, thereby, providing an alternative synthetic route to afford 3-aryl-5,7-dimethyl-1, 2, 4-triazolo[4,3-c]pyrimidines (**3**) in good yields. Encouraged from this result, we extended this approach to the synthesis of compounds **6a-b**. Structure of the title compounds was confirmed by comparing the spectral data (^{1}H NMR) and by melting points with those reported in the literature.[14] Physical data of the present study is summarized in Table 1. A plausible reaction mechanism is outlined in **Scheme 2**. The oxidation of iodobenzene **A** using *m*CPBA and *p*TSA may give the active hypervalentiodine(III) species**B** that could react with **2/5** to generate the desired product 3/6, accompanied by the liberation of iodobenzene A, which could be reoxidized to **B** by mCPBA.



Scheme 2. Proposed Catalytic Cycle

Conclusions

In summary, we have developed a new protocol for the synthesis of 3-aryl-5, 7-dimethyl-1, 2, 4-triazolo [4,3-c]pyrimidines (**3**)and 3-aryl-5,7-dimethyl-1,2,4-triazolo [4,3-a]pyrimidines (**6**) using iodobenzene as the catalyst in the presence of mCPBA as a terminal oxidant at room temperature. The reaction is simple and general to afford the target products in moderate togood yields.

Experimental

The melting points were taken in open end capillaries and are uncorrected. ^{1}HNMR spectra were recorded on BRUKER-400 MHz instrument. The hydrazones**2**and **5**required for the study were prepared by the condensation of 4-hydrazino-2,6-dimethylpyrimidine (**1)**and 2-hydrazino-4, 6-dimethylpyrimidine (**4)** respectively, with different aromatic aldehydes in ethanol with a trace of glacial acetic acid. 4-hydrazino-2, 6-dimethylpyrimidine (**1**) and 2-hydrazino-4, 6-dimethylpyrimidine (**4**) were synthesized according to the literature procedures. [16]

*General Procedure for the synthesis of **3** and **6***

To slurry of *m*-CPBA (4 eq) in dichloromethane, added p-TSA (1.0eq) and stirred it. To the stirred mixture, added PhI (10 mol%) and appropriate hydrazone (1.0eq).The reaction mixture was stirred at room temperature until the completion of the reaction. Completion of the reaction was monitored by TLC using pet ether:ethyl acetate. The mixture was the diluted with dichlormethane (CH_2Cl_2).The organic layer was first washed with sodium thiosulphate and then with sodium carbonate and finally dried over sodium sulphate. The organic layer, was filtered, evaporated and triturated with petroleum ether to give desired product **3**/**6**.

*Characterization data for products **3** and **6**:*
3a: m.p. 139-140 °C (lit m.p. 142 °C [14a]) ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3H, CH_3); 3.05 (s, 3H, CH_3); 3.91 (s, 3H, OMe); 7.04-7.07 (d, 2H, J = 9 Hz); 7.48 (s, 1H); 8.30-8.33 (d, 2H, J = 9 Hz).
3b: m.p.194-195°C (lit m.p. 197 °C [14a])
3c:m.p.157-159°C (lit m.p. 159-160 °C [14a])
3d:m.p.228-230°C (lit m.p. 229-230 °C [14a])
3e:m.p.177-178°C (lit m.p. 180 °C [14a])
3f:m.p.199-200 °C (lit m.p. 202-203 °C [14a])
6a:m.p.197-198 (decomp) °C (lit m.p. 198-199 (decomp) [14c])
6b:m.p.247-249 °C (lit m.p. 247-248 °C [14c])

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