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Regioselective dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones mediated by ceric ammonium nitrate

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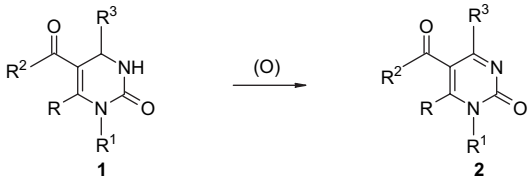
Abstract—Ceric ammonium nitrate (CAN) has been explored for the regioselective oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs). Interestingly, we obtained ethyl 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylates as the major products during the oxidation of DHPMs by CAN/AcOH at 80 °C. The reaction afforded a mixture of products while employing CAN in organic solvents without additives. However, the regioselective dehydrogenated product, ethyl 6-methyl-4-aryl(alkyl)-pyrimidin-2(1*H*)-one-5-carboxylate was obtained by performing the reaction with $NaHCO_3$. The single crystal X-ray crystallography of ethyl 6-methyl-4-(2-phenyl)-pyrimidin-2(1*H*)-one-5-carboxylate revealed that the oxidized product existed in amidic form rather than aromatized enol form of pyrimidines. The efficiency of the present protocol enabled the synthesis of structurally diverse pyrimidines in moderate to good yields under milder reaction conditions.

1. Introduction

The pyrimidine core possesses potential biological applications.[1a,b] The pyrimidine derivative MKC-442 is already in clinical trials and similar compounds are expected to inhibit the HIV virus.[1c] A series of pyrazolo[1,5-*a*]pyrimidines derivatives were shown to be potent and orally active corticotropin-releasing factor receptor antagonists.[1d] Nucleosides containing the 5-substituted pyrimidine moiety have been demonstrated to inhibit growth of murine mammary carcinoma and HIV virus.[2] Pyrimidine based molecules with extended π-systems exhibited interesting fluorescent properties.[3a] Kang et al. employed readily accessible multifunctionalized pyrimidine templates for diversity-oriented synthesis.[3b]

Recently, various protocols have been utilized for the synthesis of pyrimidines.[4] The synthesis of pyrimidin-2(1*H*)-ones by oxidation of DHPMs (Scheme 1) has rarely been explored.[5a] Unlike a large number of oxidizing agents available for achieving nearly quantitative transformation of Hantzsch dihydropyridine (DHPs) to pyridine,[5b,c] the regioselective oxidation of DHPMs is not easy.[5a] A few available literature procedures required large volumes of highly acidic and corrosive reagents or multistep strategies.[6a,7a–c] $CuCl_2$/TBHP/K_2CO_3[7d] and Jone's reagent[7e] were employed for the above conversion, but they failed to yield the desired regioselective products for oxidatively sensitive functionalities. Consequently, it is of interest to synthesize structurally diverse pyrimidines by oxidizing DHPMs under mild conditions.



Scheme 1. Oxidation of DHPMs into pyrimidin-2(1*H*)-ones.

2. Results and discussion

2.1. Screening oxidants for the regioselective oxidation of DHPMs

It is well known that DHPMs are structurally similar to DHPs.[5a] Oxidants[8a–j] that efficiently convert the DHPs into pyridine were screened for the conversion of 3,4-dihydropyrimidin-2(1*H*)-ones to pyrimidin-2(1*H*)-ones. But DHPMs are highly stable toward powerful oxidants such as PCC, MnO_2, $KMnO_4$ adsorbed on clay, chloranil, DDQ, Pd/C, and sodium nitrate in acetic acid.[6a] In addition we found that MTO,[8c] $RuCl_3$ (5 mol %)/O_2 in AcOH (room temperature),[8d] Br_2,[8e] sulfur,[8g] $FeCl_3$ (in CH_3OH and CH_2Cl_2 under room temperature and reflux),[8i] $FeCl_3$/AcOH (room temperature), and $FeCl_3$/AcOH/H_2O (1:1, room temperature) were inefficient to dehydrogenate **1a**. Concd HNO_3,[8a] MnO_2,[8b]

Keywords: Oxidation; Pyrimidines; 3,4-Dihydropyrimidin-2(1*H*)-ones; Ceric ammonium nitrate.
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$Bi(NO_3)_3$, $FeCl_3$, IBX,[8j] and CAN[8h] afforded **2a** with moderate selectivity. Among them CAN was found to be selective and its application in organic synthesis is promising (Fig. 1).[9] $FeCl_3$ and CAN furnished reasonable amount of 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylates as well (Fig. 1).

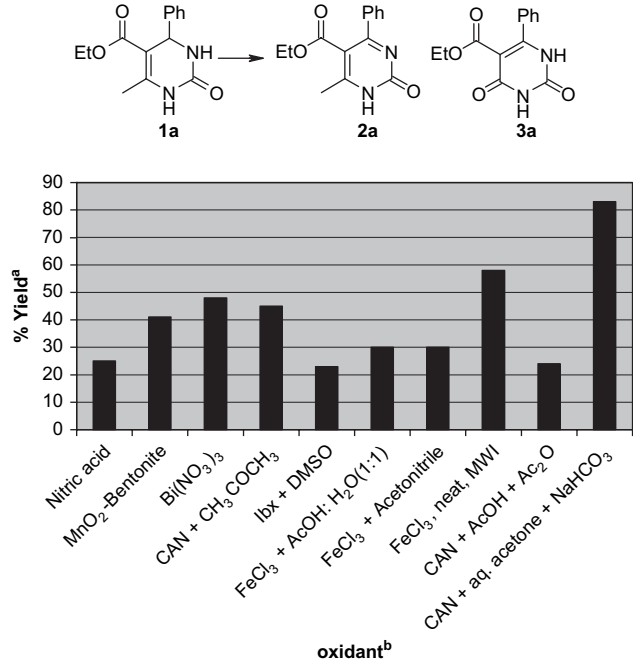
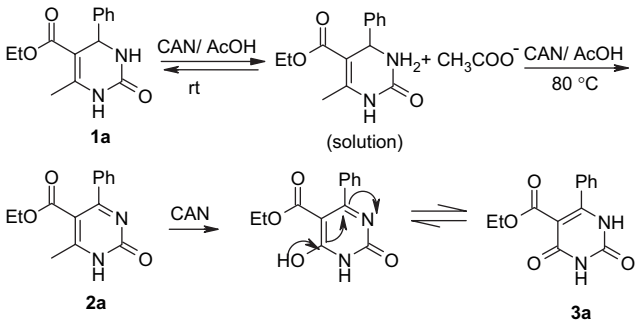


Figure 1. Screening of oxidants for the conversion of **1a** to **2a**. [a]Isolated yield. [b]The stoichiometry of oxidants was employed as used in literature for 1,4-dihydropyridine.[8a–j] And **3a** was formed in 21, 30, 10, and 33% yields, respectively, for the corresponding oxidants CAN+CH_3COCH_3, $FeCl_3$+acetonitrile, $FeCl_3$+heat+MWI, and CAN+AcOH+Ac_2O.

2.2. Synthesis of 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylates

Initially, AcOH was chosen as solvent because it dissolved DHPMs completely and is widely employed during the oxidation of DHPs.[8d,f,i,10] The addition of CAN to a stirred solution of **1a** in acetic acid did not afford the expected dehydrogenated product at ambient temperature (Scheme 2). However, the reaction furnished an unstable salt of acetic acid and **1a** in solution and was decomposed to **1a** during the workup. The trifluoroacetate salt of 4-anisyl-DHPM was trapped and characterized by NMR in solution. Ce(IV)'s inability to dehydrogenate **1a** in AcOH at room temperature might be due to coordination of **1a** with acetic acid.



Scheme 2. CAN mediated oxidation of DHPMs in AcOH.

Serendipitously, an unusual oxidation–dealkylation product, **3a**, ethyl 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylate, formed at 80 °C (Scheme 2). The ^{1}H NMR spectrum of product (**3a**) showed two new peaks with an integration of one proton each between 10 and 12 ppm. The characteristic peaks corresponding to NH(3), CH(4), and 6-methyl protons of the starting material (**1a**) (δ 8.9, 5.2, and 2.3 ppm, respectively) were absent. The *m*/*z* value of products **3a–i** is the same as DHPMs.

Therefore, an X-ray structure of **3g** was further needed to confirm the structure of the product (Fig. 2).[11] Since **3a** exhibited structural resemblance with anti-HIV agents,[1c,2] **1b–i** have been subjected to typical oxidation and the reactions afforded **3b–i** in reasonable yields (Table 1).

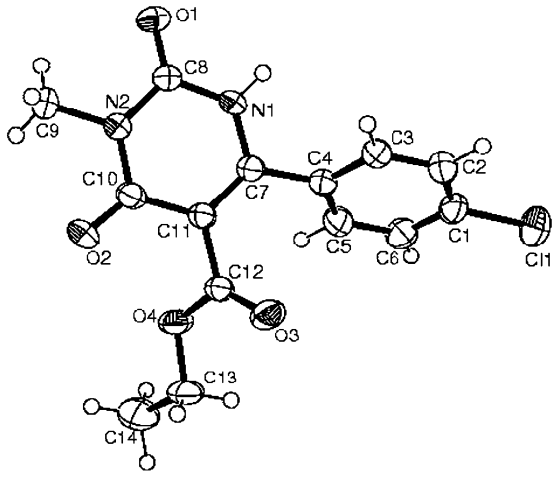
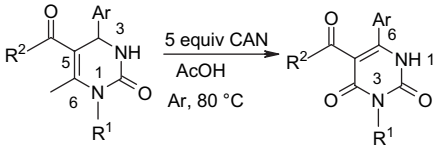


Figure 2. XRD structure of **3g**, ORTEP diagram.

Table 1. Oxidation of DHPM mediated by CAN in AcOH



Product	Ar	R^1	R^2	Time (h)	Yield (%)[a]
3a	C_6H_5	H	OEt	1.5	61
3b	3-NO_2-C_6H_4	Me	OEt	1.5	65
3c	2-NO_2-C_6H_4	H	OEt	1.0	55
3d	3-NO_2-C_6H_4	H	OEt	1.0	57
3e	4-Cl-C_6H_4	H	OEt	2.0	68
3f	1-Naphthyl	H	OEt	2.0	65
3g	4-Cl-C_6H_4	Me	OEt	1.0	62
3h	2,4-Cl_2-C_6H_3	H	Ph	2.5	63
3i	4-MeO-C_6H_4	H	OEt	1.5	68

[a] The reaction was conducted using 1 mmol of DHPM and 5 mmol of CAN in 7 mL of acetic acid at 80 °C.

2.3. Trapping of 1i as trifluoroacetate salt

To confirm the formation of a salt in acetic acid, we have dissolved **1i** in trifluoroacetic acid and a small amount of TMS was added to the solution. The ^{1}H NMR spectrum of **5** in solution showed that the CH(4) of the product has been shifted 0.5 ppm to downfield. The quaternary N(3) of **5** has