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2-Pivalamido-3*H*-pyrimidin-4-one derivatives: convenient pivalamide hydrolysis using $Fe(NO_3)_3$ in MeOH

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Abstract—A simple methodology for pivalamide (trimethylacetamide, pivaloylamino) hydrolysis has been discovered using $Fe(NO_3)_3$ in MeOH at room temperature. The pivalamido group of 2-pivalamido-3*H*-pyrimidin-4-ones or fused 2-pivalamido-3*H*-pyrimidin-4-ones such as 2-pivalamido-3*H*-quinazolin-4-ones and 2-pivalamido-3*H*-pteridines have been hydrolysed under these conditions to afford the corresponding amine.

The need for protection of amines in organic synthesis is well documented and there are many groups available to achieve this.[1] An amine protecting group, which has often been used during the synthesis of 2-amino-3*H*-pyrimidin-4-ones and fused 2-amino-3*H*-pyrimidin-4-ones such as 2-amino-3*H*-quinazolin-4-one or 2-amino-3*H*-pteridine derivatives, is the pivaloyl group. Our experience working with 3*H*-quinazolin-4-one derivatives indicated that the pivaloyl group brings the additional benefit, over other groups such as acetyl, of making these compounds more soluble in organic solvents and therefore easier to handle.

A pivalamide is stable to both mild acidic or basic environments. Usually its hydrolysis requires forceful acidic or basic conditions, although there are limited examples of successful hydrolysis using milder conditions. For example, the removal of the pivaloyl group of a series of 2-pivaloylaminopterin cycloadducts required the use of 1 N HCl at 70–80 °C.[2] Krajsovszky et al. used 20% H_2SO_4 for the hydrolysis of pivalamide derivatives.[3] Strongly acidic conditions (concentrated HCl in EtOH, heating at reflux for 5 h) were also employed by Akama et al. for pivalamide hydrolysis that led to the preparation of 2-aminoflavone derivatives.[4] Chu-Moyer et al. utilised 3 N HCl at 90 °C for 18 h to obtain 4-amino-3-hydroxypyridines from their pivalamido counterparts.[5]

Alkaline conditions were also utilised for pivalamide hydrolysis. For example, Jones et al. used 0.04 N NaOH at 50 °C (18 h) to prepare 2-aminoquinazoline-based inhibitors of thymidylate synthase from the corresponding pivalamide derivatives.[6] There have also been reports by a number of researchers describing the hydrolysis of 2-pivalamidoquinazolines or pteridines under mild conditions by utilising NH_3 in MeOH.[7,8]

In connection with work aimed at the synthesis of novel anticancer agents we found that some 2-pivalamido-3*H*-quinazolin-4-one derivatives upon treatment with $Fe(NO_3)_3{\cdot}9H_2O$ in MeOH gave the corresponding 2-amino-3*H*-quinazolin-4-one in good yield. This finding was further investigated using the 3*H*-quinazolin-4-one **1** (Table 1, entry 1) as a model compound, and it was established that the pivaloyl group could be removed by using 0.2 equiv of $Fe(NO_3)_3{\cdot}9H_2O$ in MeOH at room temperature for 24 h. Removal of the MeOH under reduced pressure, trituration of the residue with EtOH, and finally collection of the product by filtration gave **1** in 72% yield.[9] The scope of the reaction was further explored and it was found that pivalamide analogues of 2-amino-3*H*-quinazolin-4-ones (entry 2), 2-aminopteridine (entry 3), 7-methylguanine (entry 4) and 2-amino-3*H*-pyrimidin-4-one (entry 5), could also be hydrolysed under these conditions.

Keywords: 2-Pivalamido-3*H*-pyrimidin-4-ones; Hydrolysis; $Fe(NO_3)_3$.
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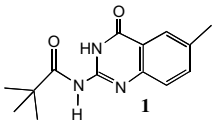
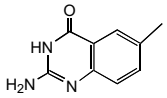
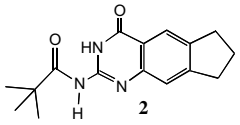
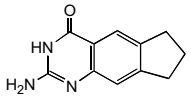
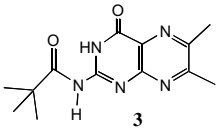
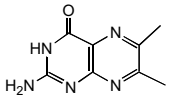
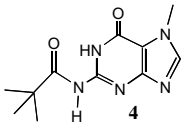
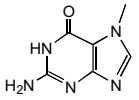
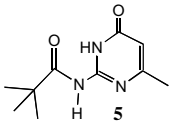
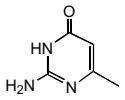
Table 1. Pivalamide hydrolysis

Entry	Pivalamide	Product	Yield (%)
1	 **1**		72
2	 **2**		78
3	 **3**		53
4	 **4**		63
5	 **5**		75

Conditions: 0.2 equiv $Fe(NO_3)_3$, MeOH, 24–40 h, rt.

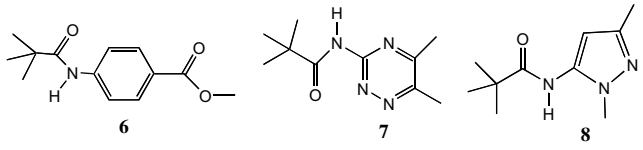


Figure 1.

However, attempts to hydrolyse the pivalamide in structures **6–8** (Fig. 1) under these conditions were unsuccessful.

In conclusion, it was found that using 0.2 equiv of $Fe(NO_3)_3$ in MeOH at room temperature provides a mild, efficient and selective method for the hydrolysis of pivaloyl groups in both fused and nonfused 2-pivalamido-3*H*-pyrimidin-4-ones.

Acknowledgements

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References and notes

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9. A typical experimental procedure is as follows: to a solution of 7-methyl-2-pivalamido-3*H*-quinazolin-4-one (0.518 g, 2.0 mmol) in MeOH (55 mL) was added $Fe(NO_3)_3{\cdot}9H_2O$ (0.161 g, 0.4 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was then removed under reduced pressure and the residue was triturated with EtOH. The precipitate was collected by filtration, dried in vacuo over phosphorous pentoxide to afford **1** as a white solid (0.250 g, 72%), ^1H NMR (250 MHz, DMSO-d_6, TMS), 3.39 (s, 3H, 6-CH_3), 7.36 (d, $J = 8.4$ Hz, 1H, 8-H), 7.63 (dd, $J = 1.5$, 8.4 Hz, 1H, 7-H), 7.81 (s, 1H, 5-H), 8.03 (br s, 2H, NH_2), 12.40 (br s, 1H, N^3–H); MS (ESI, m/z): 176 [$(M+H)^+$, 100%].