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An Efficient Synthesis of 3-Substituted 3*H*-Pyrimidin-4-ones

Jae Uk Jeong,* Xiaohong Chen, Attiq Rahman, Dennis S. Yamashita, and Juan I. Luengo

Department of Medicinal Chemistry, MMPD CEDD, GlaxoSmithKline, 1250 South Collegeville Road, Collegeville, Pennsylvania 19426

jae.u.jeong@gsk.com

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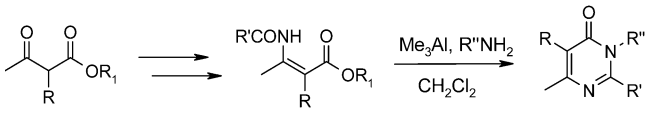
ABSTRACT



A novel and practical synthesis of 3-substituted 3*H*-pyrimidin-4-ones is described. The key step involves the cyclization of enamide esters, derived from readily available *β*-keto esters, with trimethylaluminum and various primary amines.

3-Substituted 3*H*-pyrimidin-4-ones and 3-substituted 3*H*-quinazolin-4-ones are pharmacophores present in many biologically active compounds (Figure 1). Examples include PPAR agonist **1**,[1a] angiotensin antagonist **2**,[1b] sedative-hypnotic **3**,[2a] antitussive **4**,[2b] and analgesic **5**.[2c]

There are a wide variety of methods to synthesize 3-substituted quinazolinones.[2] The known routes to 3-substituted pyrimidinones are much more limited and are depicted below (Figure 2).

Route A utilizes the Pinner condensation of *β*-keto esters with non-N-substituted amidines to pyrimidinones,[1c] followed by N-alkylation.[1d] We have examined this approach in our laboratories and confirmed that the alkylation procedure works effectively with unhindered electrophiles such as methyl iodide and allyl bromide, but it generally suffers from competing O-alkylation (even with the addition of lithium bromide)[1d] with more hindered alkylating agents. For example, when isopropyl iodide was employed, no desired N-alkylation product was observed. Route B is based on the condensation of N-substituted amidines with malonyl dichlorides. This route provides 1*H*-pyrimidine-4,6-diones that could then be further functionalized at the 6 position, but it generally produces low yields[1e] or requires lengthy reaction times[1f] and is limited in scope to highly reactive malonyl

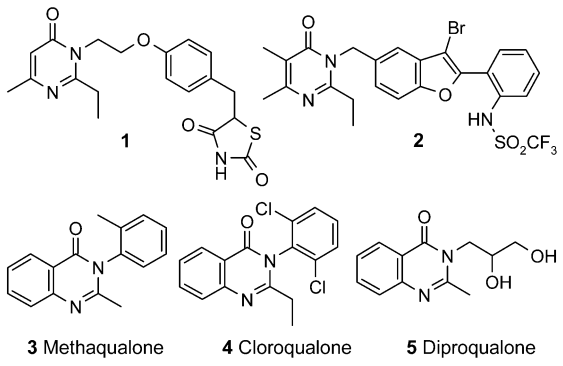


Figure 1. Biologically potent pyrimidinones and quinazolinones.

(1) (a) Madhavan, G. R.; Chakrabarti, R.; Vikramadithyan, R. K.; Mamidi, R. N. V. S.; Balraju, V.; Rajesh, B. M.; Misra, P.; Kumar, S. K. B.; Lohray, B. B.; Lohray, V. B.; Rajagopalan, R. *Bioorg. Med. Chem.* **2002**, 2671. (b) Balmforth, A. J.; Bryson, S. E.; Aylett, A. J.; Warburton, P.; Ball, S. G.; Pun, K. T.; Middlemiss, D.; Drew, G. M. *Br. J. Pharmacol.* **1994**, *112*, 277. (c) Pinner, A. *Chem. Ber.* **1889**, *22*, 1612. (d) Salimbeni, A.; Canevotti, R.; Paleari, F.; Poma, D.; Caliari, S.; Fici, F.; Cirillo, R.; Renzetti, A. R.; Subissi, A.; Belvisi, L.; Bravi, G.; Scolastico, C.; Giachetti, A. *J. Med. Chem.* **1995**, *38*, 4806. (e) Jezewski, A.; Jurczak, J.; Lidert, Z.; Tice, C. M. *J. Heterocycl. Chem.* **2001**, *38*, 645. (f) Sitte, A.; Paul, H. *Chem. Ber.* **1969**, *102*, 615. (g) Taylor, E. C.; Zhou, P.; Tice, C. M. *Tetrahedron Lett.* **1997**, *38*, 4343. (h) Takahashi, T.; Hirokami, S.; Nagata, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2653. (i) Yamamoto, Y.; Morita, Y.; Minami, K. *Chem. Pharm. Bull.* **1986**, *34*, 1980.

(2) (a) Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campell, J. A.; Greenwood, T. D. *J. Med. Chem.* **1990**, *33*, 161. (b)Buzas, A.; Hoffmann, C. *Bull. Soc. Chim. Fr.* **1959**, 1889. (c) Welch, W. M.; Ewing, F. E.; Huang, J.; Menniti, F. S.; Pagnozzi, M. J.; Kelly, K.; Seymour, P. A.; Guanowsky, V.; Guhan, S.; Guinn, M. R.; Critchett, D.; Lazzaro, J.; Ganong, A. H.; DeVries, K. M.; Staigers, T. L.; Chenard, B. L. *Bioorg. Med. Chem. Lett.* **2001**, 177.

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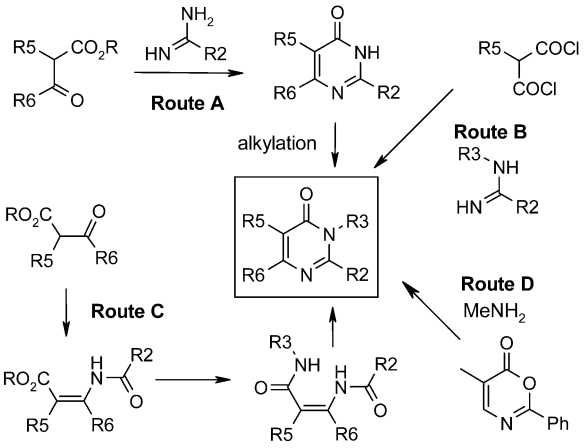


Figure 2. Synthetic methods for pyrimidinones.

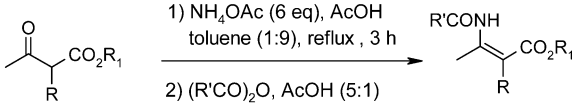
dichlorides.[1g] Route C involves the dehydration of an enediamide. An example has been reported in which an enediamide (Figure 2, Route C, R2 = R3 = R5 = Me, R6 = *t*-Bu) is cyclized to a 3-substituted pyrimidinone by refluxing in ethanol for 5 days, but the isolated yield in this case is only 12%.[1h] In Route D, an oxazinone intermediate is used to form an enediamide in situ, which then undergoes cyclization as in Route C. An example starting with oxazinone, 5-methyl-2-phenyl-6*H*-1,3-oxazin-6-one (Figure 2), and methylamine in ethanol has been published, but the scope of the reaction has not been extensively examined.[1i]

In this paper, we describe a novel and efficient synthesis of 3-substituted pyrimidinones from β-keto esters, acid anhydrides, trimethylaluminum, and various primary amines (Figure 2, Route C). We also delineate the syntheses of oxazinones and quinazolinones using either dimethylaluminum amides or trimethylaluminum.

Enamide esters **7** were prepared for this study in high isolated yields with a high *Z*/*E* ratio in a single reaction flask by a two-step process (Table 1). β-Keto esters **6**[3] were combined with ammonium acetate in refluxing acetic acid and toluene to form eneamines.[4] Following Dean−Stark trap removal of water, ammonium acetate, acetic acid, and most of the toluene (without aqueous workup), the enamines were acylated with acid anhydrides and acetic acid at 70 °C to produce enamide esters **7**.[5] The acylation step could alternatively be achieved under basic conditions with pyridine in refluxing THF, but generally gave lower yields.[6]

Enamide esters **7** were converted into pyrimidinones **8** using dimethylaluminum amides. For example, treatment of enamide ester **7a** with 3 equiv of dimethylaluminum amide[7]

Table 1. Preparation of Enamide Esters **7** from β-keto Esters



6 **7**

6	**7**	*Z*:*E* ratio[a]	yield (%)[b]
6a	**7a**	91:9	69
6b	**7b**	95:5	87
6c	**7c**	98:2	81
6d	**7d**	only Z	81

[a] Ratio was determined after isolation by flash column chromatography. [b] Overall isolated yield of (*Z*)-isomers without purification of intermediates.

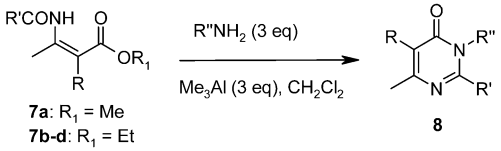
(formed in situ from trimethylaluminum and aniline in a 1:1 ratio at room temperature in methylene chloride with evolution of methane) for 5 h at room temperature provided the desired pyrimidinone **8a** in 84% yield (Table 2, entry 1). Interestingly, when enamide ester **7a** was stirred with 1 equiv of dimethylaluminum amide for 23 h at room temperature, only 50% conversion to product **8a** was observed (with 50% recovery of enamide ester **7a**). Even after reflux for 6 h, the ratio of enamide ester **7a** and pyrimidinone **8a** did not change significantly. However, the reaction with 2 equiv of dimethylaluminum amide for 20 h at room temperature provided an 87% yield of product **8a** along with 10% of enamide ester **7a**. These results suggest that at least 2 equiv of dimethylaluminum amide reagent are required for this reaction to run to completion.

Using our optimized reaction conditions with 3 equiv of trimethylaluminum and 3 equiv of various primary amines, including aromatic amines, bulky amines such as cyclohexylamine, amines containing an alkoxy group, as well as hydrazine, afforded good to excellent isolated yields of 3-substituted pyrimidinones **8** from a structurally diverse set of enamide esters **7a**−**d** (Table 2).[8,9a] In some cases, higher reaction temperatures were used to shorten reaction times. For example, 3-ethoxypropylamine (Table 2, entry 8) and dimethyl hydrazine (Table 2, entry 9) reacted sluggishly at room temperature, but proceeded smoothly in refluxing methylene chloride with high yields (70−77%). Enamide ester **7a** was processed to pyrimidinone **8b** within 1 h in refluxing methylene chloride (Table 2, entry 3) compared to 7 h at room temperature (Table 2, entry 2).

We also explored the reactivity of an (*E*)-enamide ester. Employing the standard reaction conditions led to the

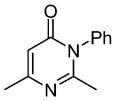
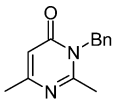
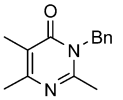
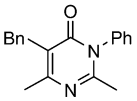
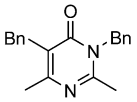
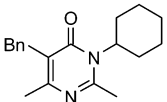
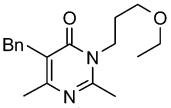
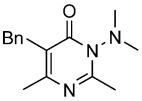
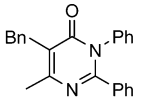
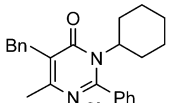
(3) (a) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087. (b) Taber, D. F.; You, K.; Song, Y. *J. Org. Chem.* **1995**, *60*, 1093.
(4) Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Philips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.
(5) Representative experimental procedure for **7a** is described in Supporting Information.
(6) (a) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543. (b) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907.
(7) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

Table 2. Cyclization to 3-Substituted Pyrimidinones 8



7a: R_1 = Me
7b-d: R_1 = Et

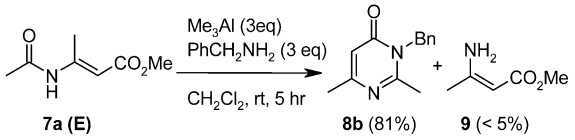
8

entry	7	R"	temp[a], time	product	yield(%)
1	**7a**	Ph	rt, 5h	 **8a**	84[b]
2	**7a**	$PhCH_2$	rt, 7h	 **8b**	85[b]
3	**7a**	$PhCH_2$	40 °C, 1h	**8b**	83[b]
4	**7b**	$PhCH_2$	rt, 5h	 **8c**	74
5	**7c**	Ph	rt, 4h	 **8d**	98
6	**7c**	$PhCH_2$	rt, 6h	 **8e**	87
7	**7c**	c-Hex	rt, 6h, & 40 °C, 1h	 **8f**	64
8	**7c**	$EtO(CH_2)_3$	40 °C, 20h	 **8g**	77
9	**7c**	Me_2N	40 °C, 20h	 **8h**	70
10	**7d**	Ph	rt, 4h	 **8i**	72
11	**7d**	c-Hex	83 °C, 4h	 **8j**	62

[a] All reactions were carried out in CH_2Cl_2 except entry 11, which was carried out in $ClCH_2CH_2Cl$. [b] Enamine **9** was obtained in <5% yields

transformation of the (*E*)-isomer of the enamide ester **7a**(*E*) into pyrimidinone **8b** in 81% yield along with a small amount of deacetylated enamine **9** (Scheme 1). Furthermore, the reaction with the *E*/*Z* mixture of the enamide esters **7a**/**7a**(*E*) without purification starting from β-keto ester **6a** under the standard reaction conditions provided the desired product **8a** in good yield (52% for three steps).[9b]

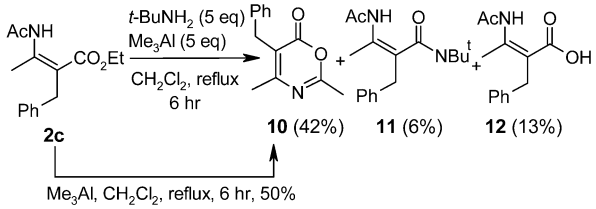
Scheme 1



7a (E) **8b** (81%) **9** (< 5%)

We further investigated the scope of our pyrimidinone synthesis methodology by assessing sterically hindered amines. For instance, when enamide ester **2c** was subjected to the standard conditions with *tert*-butylamine, there was no reaction (only starting material without any desired product formation) at room temperature. In refluxing methylene chloride for 6 h, there was still no desired product observed. Instead, oxazinone **10**, enediamide **11**, and carboxylic acid **12** were isolated following aqueous workup and silica gel chromatography (Scheme 2). Oxazinone **10** was also made from enamide ester **2c** with 3 equiv of trimethylaluminum (no amine) in refluxing methylene chloride. But, the resultant oxazinone **10** was unstable and slowly hydrolyzed to carboxylic acid **12** at room temperature.

Scheme 2



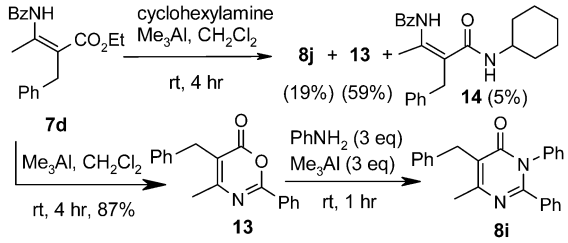
When enamide ester **7d** was exposed to the standard reaction conditions with cyclohexylamine at room temperature, only 19% of the desired compound **8j** was isolated along with oxazinone **13** in 59% yield and enediamide **14** in 5% yield (Scheme 3). Unlike oxazinone **10**, oxazinone **13** was found to be chemically stable.

Oxazinone **13** could alternatively be fashioned from enamide ester **7d** and trimethylaluminum (no amine) at room temperature. Following purification by silica gel column chromatography, oxazinone **13** was successfully converted into pyrimidinone **8i** from aniline and trimethylaluminum at room temperature in 82% yield (Scheme 3). Pyrimidinone **8j** was obtained from enamide ester **7d** with trimethylaluminum and cyclohexylamine in refluxing 1,2-dichloroethane

(8) All pyrimidinones were characterized by ^1H NMR, ^{13}C NMR, IR, and LCMS.

(9) (a) Representative experimental procedure for pyrimidinones **8a** is described in Supporting Information. (b) Experimental procedure is described in Supporting Information.

Scheme 3



(Table 2, entry 11). Cyclization using a branched amine like cyclohexylamine could be achieved by raising the reaction temperature, but in the case of the more hindered *tert*-butylamine, cyclization could not be realized.

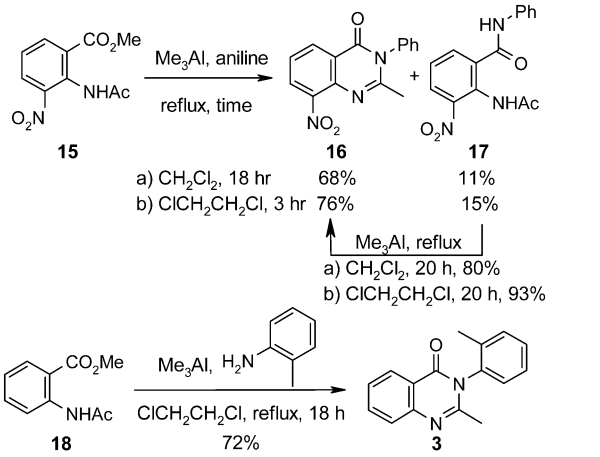
These results help to rationalize the requirement of 2 equiv of dimethylaluminum amide for the reaction to run to completion. Use of 1 equiv forms oxazinone intermediates from the esters and at least another equivalent forms the diamides, which undergo subsequent cyclization to pyrimidinones.

Finally, we extended our investigation to the synthesis of quinazolinones. Applying our standard conditions in refluxing methylene chloride, benzoate **15** was converted to quinazolinone **16** in 68% yield, accompanied by 11% yield of benzodiamide **17**. The isolated yield of **16** was increased to 76% by changing the reaction conditions to refluxing 1,2-dichloroethane. Also, exposure of benzodiamide **17** to 3 equiv of trimethylaluminum (no amine) in refluxing methylene chloride or 1,2-dichloroethane provided quinazolinone **16** in 80 and 93% yields, respectively.[10] Methaqualone **3** was efficiently prepared from commercially available benzoate **18** with 2-methyl aniline and trimethylaluminum in one step in 72% yield (Scheme 4).[11]

(10) Reactions were monitored and yields were reported by LCMS.

(11) Trace amount (less than 5%) of 2-acetylamino-*N*-*o*-tolyl-benzamide (not shown) was also isolated.

Scheme 4



Dimethylaluminum amides have been developed for the preparation of amides from esters.[7] This transformation plays a key role in our synthesis of 3-substituted pyrimidinones from enamide esters. We have further discovered that dimethylaluminum amides or trimethylaluminum can also promote the cyclization of enamide esters to oxazinones, enediamides to pyrimidinones, and benzodiamides to quinazolinones. These reactions can be conducted in tandem and can provide access to a broad scope of these heterocyclic systems in high yields.

Acknowledgment. We thank Priscilla Offen and Bing Wang for their assistance with characterization of compounds by NMR.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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