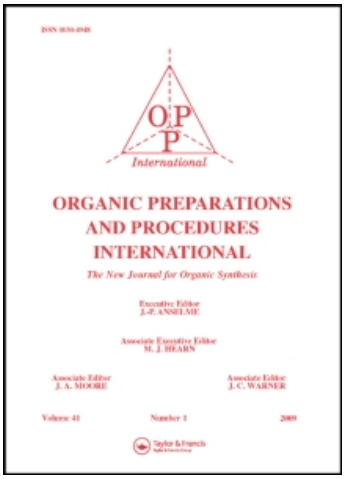


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A FACILE BASE CATALYZED CONDENSATION FOR THE SYNTHESIS OF FUSED PYRIMIDINE-2-CARBOXYLIC ACID ESTERS

Susumu Nakanishi[a]; Stephen S. Massett[a]
[a] Central Research, Pfizer Inc., Groton, Conn.

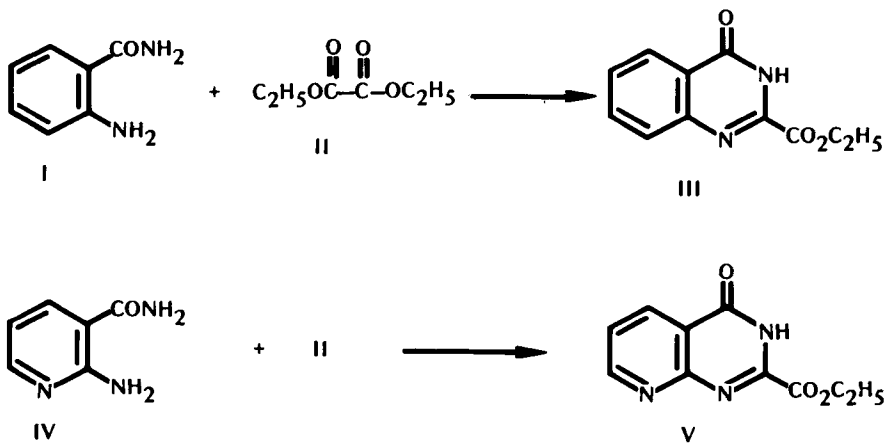
To cite this Article Nakanishi, Susumu and Massett, Stephen S.(1980) 'A FACILE BASE CATALYZED CONDENSATION FOR THE SYNTHESIS OF FUSED PYRIMIDINE-2-CARBOXYLIC ACID ESTERS', Organic Preparations and Procedures International, 12: 3, 219 — 223
To link to this Article: DOI: 10.1080/00304948009458552
URL: http://dx.doi.org/10.1080/00304948009458552

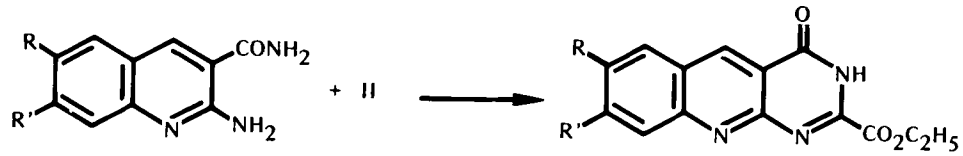
ORGANIC PREPARATIONS AND PROCEDURES INT. 12(3-4), 219-223 (1980)

A FACILE BASE CATALYZED CONDENSATION FOR THE SYNTHESIS OF FUSED PYRIMIDINE-2-CARBOXYLIC ACID ESTERS

Susumu Nakanishi* and Stephen S. Massett
Central Research, Pfizer Inc., Groton, Conn. 06340

Synthesis of ethyl 3,4-dihydro-4-oxoquinazoline-2-carboxylate (III) by the fusion of anthranilamide (I) with diethyl oxalate is known.[1] However, the severe conditions (melt held at 170°-180° for 6 hrs) afford only modest yields (57%) of desired material (III).[1] We report herein an alternative, facile and mild cyclocondensation method which is carried out in ethanol in the presence of sodium ethoxide. The method[2] provides dependable and high yields of the condensed carbethoxy compounds. This method has general applicability for the amino-carboxamide ring-closure with diethyl oxalate and has been extended to the condensation of aminonicotinamide as well as aminoquinoline carboxamides as shown below.





VI R = R' = H
VII R = R' = OCH_3
VIII R = Cl, R' = H

IX R = R' = H
X R = R' = OCH_3
XI R = Cl, R' = H

The improved yields obtained using this base catalyzed condensation are illustrated in Table I.

Table I

Improved Yields Obtained Using NaOEt Catalyzed Condensation of Amino-Carboxamides with Diethyl Oxalate at Ambient Temperatures

	% Yields	
Product	*"Old" Procedure*[a]	*"New" Procedure*[2]
III	57%[1]	99%
V	30%[3a]	90%
IX	45%[3a]	92%
X	15%[3b]	99.5%
XI	37%[3b]	96%

[a]This procedure involves heating the o-aminoarylcarboxamide with diethyl oxlate (neat) or in a high boiling solvent such as xylene or DMF.

The sodium ethoxide used to catalyze the reaction is conveniently prepared *in situ* by reaction of ethanol with sodium hydride or sodium metal. The use of three equivalents of sodium ethoxide to effect the condensation appears optimal. With two equivalents or less the reaction did not proceed to completion. Sodium hydroxide in ethanol did not catalyze the reaction.

6-Chloro-2-aminoquinoline-3-carboxamide (VIII) was found to be the most reactive compound and the condensation was completed within 15 minutes at 20-25°. The slowest reacting compound was anthranilamide (I), where condensation required 5 hrs at 70-75° or 48 hrs at 20-25°. The yields of the condensed products were over 90%.

EXPERIMENTAL

Ethyl 3,4-dihydro-4-oxoquinazoline-2-carboxylate (III): — A mixture of 6.8 g (50 mmol) of anthranilamide (I), 14.6 g (0.1 mol) of distilled diethyl oxalate, and 1.2 g (0.15 mol) of NaOEt in 120 ml EtOH was stirred at 20-25° for 48 hrs[4] under N_2 atmosphere. The reaction mixture was acidified with 15 ml of glacial HOAc and the resulting solid was collected by filtration, washed with EtOH, and dried to give 10.8 g (99%) of crude (III), m.p. 178-180°. Lit.[1] m.p. 179-180°. Recrystallization from EtOH gave 9.8 g (90%) of (III), m.p. 185-186°, ν^{KBr} 5.78 (ester), 5.99 (amide), 6.25, and 8.55 μ. λ_{max}^{EtOH} 229 nm, $E_{1cm}^{1\%}$ = 896; 298 nm, $E_{1cm}^{1\%}$ = 455; **Anal.** Calcd. for $C_{11}H_{10}N_2O_3$; C, 60.54; H, 4.62; N, 12.84; Found: C, 60.46; H, 4.48; N, 12.65.

Ethyl 3,4-dihydro-4-oxopyrido[2,3-d]pyrimidine-2-carboxylate (V)[3a] — Aminonicotinamide (IV) was prepared from 2-aminonicotinic acid by the procedure of Kirpal[6]. Using the procedure of the preceding example, a mixture of 27.4 g (0.2 mol) of (IV), 88.6 g (0.6 mol) of diethyl oxalate, and 13.9 g (0.6 g-atm) of Na in 800 ml of EtOH was heated at 70-75° for 4 hr. Neutralization with HOAc resulted in 39.5 g (90%) of the desired compound (V), m.p. 190-192°, identical with authentic V[3a]. **Anal.** Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.71; Found: C, 54.52; H, 4.06; N, 19.66.

Ethyl 3,4-dihydro-4-oxopyrimido[4,5-b]quinoline-2-carboxylate (IX)[3a] — 2-Aminoquinoline-3-carboxamide (VI)[7], 37.4 g (0.2 mol), was treated in the same manner as the preceding example and gave 49.5 g (92%) of the desired compound (IX), m.p. 247-248° (dec), identical with the compound (IX) produced by a previously known method.[3a] **Anal.** Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61; Found: C, 62.41; H, 4.05; N, 15.54.

Ethyl 7,8-dimethoxy-3,4-dihydro-4-oxopyrimido[4,5-b]quinoline-2-carboxylate (X)[3b] — A 3 L flask, equipped with a stirrer, thermometer, condenser, and N_2 gas inlet was charged with 180 ml of EtOH. Under a dry N_2 atmosphere, 13.9 g (0.6 mol) of Na metal was added, with occasional cooling to prepae NaOEt *in situ*. After all the

Na was dissolved, 88.6 g (0.6 mol) of redistilled diethyl oxalate was added in one portion to the clear solution at 20-25° and 50 g (0.2 mol) of 6,7-dimethoxy-2-aminoquinoline-3-carboxamide (VII)[3b] was added in several portions, maintaining the reaction temperature at 30°-35°. The stirred reaction mixture was then heated at 70-75° for 3 hr,[4] cooled to 30°-35°, and 90 g (1.5 mol) of glacial HOAc was added. The resulting light yellow solid was warmed[5] to 70-75° for 15 minutes, then cooled to 60° and filtered. After washing well with warm (40-45°) EtOH, the solid was dried, yielding 66.2 g (99.5%) of crude (X), m.p. 250-255° (dec.). Recrystallization from either EtOH or N-methyl-2-pyrrolidone gave 46.1 g (78%) of pure X, identical with authentic product[3b]: m.p. 275° (dec), Lit.[3b] 272-273° (dec), ν^{KBr} 5.73, 5.95, 6.3 and 6.7 μ. $\lambda_{max}^{CHCl_3}$ 382 nm $E_{1cm}^{1\%}$ = 640. **Anal.** Calcd. for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.78; Found: C, 58.34; H, 4.57; N, 12.80.

Ethyl 7-Chloro-3,4-dihydro-4-oxopyrimido[4,5-b]quinoline-2-carboxylate (XI)[3b] — To a solution of 6.7 g (30 mmol) of 6-chloro-2-aminoquinoline-3-carboxamide[3b] in 150 ml EtOH containing 4.1 g (60 mmol) of NaOEt (prepared *in situ* with 1.4 g of Na metal) was added, at room temp., 8.8 g (60 mmol) of diethyl oxalate. After allowing the reaction mixture to stand at 20° to 25° for 45 min,[6] 9 g (0.15 mol) of glacial HOAc was added and the resulting solid was granulated at 5° to 10° for 15 min, then collected by filtration, washed with EtOH and dried at 65-70° to give 8.7 g (96%) of the desired compound (XI), m.p. 239-240° (dec.). ν^{KBr} 5.65, 5.95, 6.3, 6.85, 7.3 μ. **Anal.** Calcd. for $C_{14}H_{10}N_3O_3Cl$: C, 55.36; H, 3.32; N, 13.84; Cl, 11.68; Found: C, 55.17; H, 3.31; N, 13.76; Cl, 11.64.

REFERENCES

1. B.R. Baker and P.I. Almaula; J. Org. Chem., **27**, 4672 (1962).

2. S. Nakanishi; Pfizer Inc. NL-7,603,293 (1976).

3a. T.H. Althuis, P.F. Moore and H.-J. Hess; J. Med. Chem., **22,** 44 (1979).
b. T.H. Althuis, S.B. Kadin, L.J. Czuba, P.F. Moore and H.-J. Hess; J. Med. Chem., **23,** in press (1980); T.H. Althuis, L.J. Czuba, H.-J. Hess and S.B. Kadin; U.S. Patent 3,974,161 (1976).

4. The reaction was monitored by thin layer chromatography using a Brinkman F524 plate and chloroform-ethanol (8:2 v/v) system, R_f = 0.95.

5. Heating of the thick mass of solid which initially precipitates gave a mixture that was more easily stirred and which filtered rapidly.

6. A. Kirpal; Monatsh., **21,** 957 (1900); H.H. Fox; J. Org. Chem., **17,** 547 (1952).

7. E.C. Taylor, Jr. and N.W. Kalenda; J. Org. Chem., **18,** 1755 (1953); J. Am. Chem. Soc., **78,** 5108 (1956).

8. The reaction was monitored by thin layer chromatography using silica gel GF plate and chloroform-ethanol (95:5 v/v) system.

(Received August 9, 1979; in revised form January 2, 1980)