Harry L. Yale and E. R. Spitzmiller

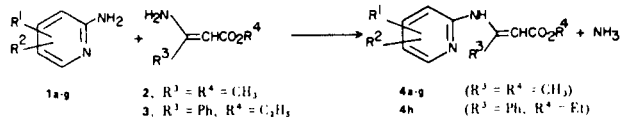
The Squibb Institute for Medical Research, Princeton, New Jersey 08540

Received May 23, 1977

Transenamination, a reaction apparently not previously described in the literature, has been employed to prepare a series of 2-pyridylenamines. The products were formed in 11-78% yield by the reaction of substituted 2-aminopyridines, **1a-g**, and either methyl 3-aminocrotonate, **2**, or ethyl 3-aminocinnamate, **3**, in anhydrous toluene, under reflux. Data from these reactions would suggest that the reaction rates and consequently, the yields, were adversely affected by substitution that served to decrease the basicity of the amino group in either reactant.

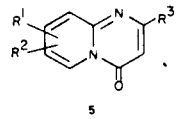
J. Heterocyclic Chem., **14**, 1419 (1977)

Transenamination, the exchange of the amine portion of an enamine by a different amine, is a reaction that has not, apparently, been reported in the literature (1,2,3). In this Note, we are describing the prototype application of this procedure, namely, the reaction between several substituted 2-aminopyridines, **1a-g**, and methyl 3-aminocrotonate, **2**, or ethyl 3-aminocinnamate, **3**, two examples of conjugated, functionalized enamines (4), to prepare the functionalized 2-pyridylenamines, **4a-h**, a species capable of undergoing facile annulation to the 4*H*-pyrido-[1,2-*a*]pyrimidin-4-one heterocycle, **5** (5,6).



1a-g **2**, $R^3 = R^4 = CH_3$; **3**, $R^3 = Ph$, $R^4 = C_2H_5$ **4a-g** ($R^3 = R^4 = CH_3$) **4h** ($R^3 = Ph$, $R^4 = Et$)

1a, **4a**, $R^1 = 3\text{-}CH_3$, $R^2 = H$
1b, **4b**, $R^1 = 5\text{-}CH_3$, $R^2 = H$
1c, **4c**, $R^1 = 6\text{-}CH_3$, $R^2 = H$
1d, **4d**, $R^1 = 5\text{-}Br$, $R^2 = H$
1e, **4e**, $R^1 = 5\text{-}Cl$, $R^2 = H$
1f, **4f**, $R^1 = 3\text{-}Cl$, $R^2 = 5\text{-}CH_3$
1g, **4g**, $R^1 = 3\text{-}CH_3$, $R^2 = 5\text{-}Cl$

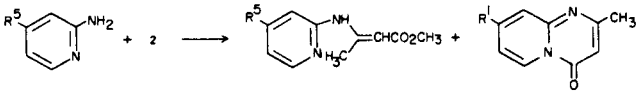


5

The transenamination reactions were carried out in toluene under reflux, while purging continuously with a slow stream of nitrogen, for periods of 3-7 days. During these prolonged heating periods, ammonia was evolved from all of the reactions and was still being evolved when the heating was terminated. That both of the reactants were stable under these experimental conditions was attested to by their recovery during the workup and isolation of the enamines. These exploratory studies would suggest that a decrease in the basicities of the amino group in either reactant adversely affected the reaction rates and, consequently, the yields of the enamines. For example, **3** was significantly less reactive than was **2** toward the same substrate, **1d**, and **1f** was far less reactive than was **1g** toward the common substrate, **2**.

The enamines being reported at this time were found to be stable compounds that were unaffected by recrystallization or storage. Three of them were isolated *via* distillation, *in vacuo*, at still head temperatures up to 152°/5 mm; all three distilled in a 1-2° range with no evidence of degradation or cyclization.

When either 2-aminopyridine or 2-amino-4-methylpyridine was reacted with **2**, a mixture, in each instance, of the enamine and cyclized derivatives, **1h** and **6**, and **1i** and **7**, respectively, were obtained.



1h, $R^5 = H$ **6**, $R^1 = H$
1i, $R^5 = CH_3$ **7**, $R^1 = CH_3$

That the transenaminamination reaction may be of general application can be deduced from our observation that aniline and **2**, for example, under the conditions described in this paper, also give the corresponding enamine in 56% yield.

EXPERIMENTAL

The ir, and pmr spectra and the elemental analyses were obtained from the Analytical Department of This Institute. The mp's were taken in capillary tubes in an electrically heated oil bath and are uncorrected.

The procedure described below for the preparation of **4d** is typical. When distillation was employed, the toluene solution remaining after the indicated heating time was completed was filtered with the aid of Hyflo, the filtrate was concentrated *in vacuo*, and the residue distilled; unchanged reactants were obtained as a forerun and were identified from their ir spectra. The relevant data for the other enamines are summarized in Table I.

Methyl 3-[(5-Bromo-2-pyridinyl)amino]-2-butenoate, **4d**.

A solution of 8.6 g. (0.05 mole) of 2-amino-5-bromopyridine, 6.3 g. (0.055 mole) of methyl 3-aminocrotonate, and 150 ml. of anhydrous toluene was heated under anhydrous conditions under reflux while being purged with a slow stream of dry nitrogen gas for 4 days, filtered with the aid of Hyflo, and the filtrate concentrated to dryness *in vacuo*. The residue, 14.2 g., m.p. 55-85° was recrystallized from 65 ml. of acetonitrile to give 8.2 g. (60% yield) of **4d**, m.p. 92-93°, ir (deuteriochloroform): ν 3400(s), 3280(s), 1710(s), 1680(s), 1640(w), 1500(s) cm^{-1}; pmr (deuteriochloroform): δ 2.45 (2, 3H, C*H*$_3$-C); 3.65 (s, 3H, C*H*$_3$O), 4.70 (s, 1H, C=C*H*), 6.70 [d (J = 6 Hz), *H* at position -3], 7.65 (q (J = 2.6 Hz), 1H, *H* at position -4], 8.28 [d (J = 2 Hz), 1H, *H* at position -6], 11.05 [s, 1H, NH (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{10}H_{11}BrN_2O$: C, 44.30; H, 4.09; N, 10.34; Br, 29.48. Found: C, 44.45; H, 4.07; N, 10.50; Br, 29.71.

Table I

2-Pyridylenamines

Compound No.	Heating time, days	Mol. Formula	Yield, %	M.p., °C	B.p., °C/mm	Recrystallization Solvent	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
4a	4	$C_{11}H_{14}N_2O_2$	63	69-71	109-110/0.3	--	64.06	6.84	13.58	--	63.99	7.05	13.86	--
4b	3	$C_{11}H_{14}N_2O_2$	52	66-68	--	Methanol	64.06	6.84	13.58	--	64.24	6.63	13.67	--
4c	7	$C_{11}H_{14}N_2O_2$	78	33-35	150-152/5.0	--	64.06	6.84	13.58	--	64.10	6.93	13.59	--
4e	7	$C_{10}H_{11}ClN_2O_2$	69	90.92	--	Pentane (a)	52.96	4.89	12.36	15.63 (b)	53.15	4.98	12.41	15.41
4f	7	$C_{11}H_{13}ClN_2O_2$	75	125-127	--	Pentane	54.88	5.44	11.63	14.73	54.80	5.30	11.87	14.66
4g	7	$C_{11}H_{13}ClN_2O_2$	15	93.95	132-133/0.3	--	54.88	5.44	11.63	14.73	55.06	5.33	11.65	14.48
4h	5	$C_{16}H_{15}BrN_2O_2$	11	110-112	--	Pentane	55.35	4.35	8.07	23.01 (c)	55.10	4.42	8.05	22.97

(a) The material that was insoluble in the pentane used to recrystallize **4e** weighed 0.2 g.; recrystallization from 30 ml. of toluene gave 0.10 g. (0.6% yield) of **6**, m.p. 233-235°. *Anal.* Calcd. for $C_{14}H_{12}Cl_2N_4O$: C, 52.03; H, 3.74; N, 17.34; Cl, 21.94. Found: C, 52.28; H, 3.49; N, 17.17; Cl, 21.68.

(b) Calcd.: N.E., 227; Found: N.E. ($HClO_4$ in glacial acetic acid), 222. (c) Br.

6

Methyl 3-[(2-Pyridinyl)amino]-2-butenoate, **1h**, and 4*H*-Pyrido-[1,2-*a*]pyrimidin-4-one, **6**.

A solution of 4.7 g. (0.05 mole) of 2-aminopyridine, 6.3 g. (0.055 mole) of **2**, and 150 ml. of anhydrous toluene was reacted as in **4d** above for 7 days, filtered while hot, the filtrate concentrated to dryness *in vacuo*, and the residue distilled to give 6.4 g. of a mixture of an oil and solid, b.p. 99-102° (0.2 mm). The pmr spectrum of this material showed a ratio of the integrated signals at δ 4.67 and δ 6.35 of 14:9, respectively, suggesting that the mixture was 61% **1h** and 39% **6**. The product was filtered with suction on a coarse sintered glass funnel to give 3.7 g. of crude **1h** as the filtrate and 2.6 g. of crude **6** as a granular solid (the ratio was now 58:42). The oil was distilled to give 3.5 g. (36% yield) of **1h** as a pale yellow oil, b.p. 110° (0.1 mm), n_D^{22} 1.6106.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57; N.E., 192. Found: C, 62.85; H, 6.22; N, 14.28; N.E. ($HClO_4$), 182.

The crude **6** was recrystallized from 100 ml. of hexane to give 2.1 g. (26% yield) of pure **6**, m.p. 118-119° whose ir and pmr spectra were identical with those obtained with authentic **6** (5).

Methyl 3-[(4-Methyl-2-pyridinyl)amino]-2-butenoate, **1i**, and 8-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **7**.

A solution of 5.4 g. (0.05 mole) of 2-amino-4-methylpyridine, 6.3 g. (0.055 mole) of **2**, and 150 ml. of anhydrous toluene was reacted as in **4d** above for 6 days, filtered while hot, and the filtrate concentrated to dryness *in vacuo* to give 11.4 g. of an oily solid. The pmr spectrum of this material indicated a 32%:68% mixture, respectively, of **1i** and **7**. The entire crude product and 200 ml. of pentane was stirred and heated under reflux for 1 hour, cooled, and the solid filtered to give 6.5 g. of crude **7**, m.p. 118-127°. Recrystallization from 200 ml. of cyclohexane gave 4.3 g. (49% yield) of **7**, m.p. 128-130°, whose ir and pmr spectra were identical with authentic **7** (5). The pentane filtrate (see above) was concentrated to dryness and the residue distilled to give 2.6 g. (25% yield) of **1i**, as a pale yellow oil, b.p. 120° (0.1 mm), n_D^{22} 1.5963.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58; N.E., 206. Found: C, 63.71; H, 6.92; N, 13.25; N.E. ($HClO_4$), 211.

Methyl 3-(Phenylamino)-2-butenoate, **8**.

A solution of 4.6 g. (0.05 mole) of reagent grade aniline and 6.3 g. (0.055 mole) of **2** in 150 ml. of anhydrous toluene was heated as in **4d** for 5 days, the hot solution was filtered, and the filtrate concentrated *in vacuo*. The residual oil solidified to a mixture of a yellow solid and dark oil. At room temperature, the mixture was filtered through a coarse sintered glass funnel to give 7.0 g. of crude **8**, m.p. 42-45°. The solid was recrystallized from 28 ml. of 1,3-dimethylcyclohexane to give 5.4 g. (56% yield) of pure **8**, m.p. 43-45°, ir (potassium bromide): ν 3200(m), 1650(s), 1605(s), 1590(s), 1500(m), 1480(s), 1450(m), 1430(m) cm^{-1}; pmr (deuteriochloroform): δ 2.02 [d (J = 3 Hz)], 3H, CH_3C, 3.70 (s, 3H, CH_3O), 4.73 (s, 1H, C=C*H*), 6.70-7.50 (m, 5H, 5 Ar-*H*).

Anal. Calcd. for $C_{11}H_{13}N_2O$: C, 69.08; H, 6.85; N, 7.32. Found: C, 68.85; H, 6.78; N, 7.26.

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(3) Personal Communications from Drs. J. Szmuszkovicz and U. K. Pandit.

(4) The term, "conjugated functionalized enamines", has been used by Dr. U. K. Pandit in an extensive series of papers on the reactions of enamines derived from β-keto esters; *cf.* H. Bieräugel, J. M. Akkerman, J. C. Lapierre Armande, and U. K. Pandit, *Rec. Trav. Chim.*, **95**, 266 (1976).

(5) H. L. Yale, B. Toeplitz, J. Z. Gougoutas, and M. Puar, *J. Heterocyclic Chem.*, **10**, 123 (1973). H. L. Yale, *ibid.*, **11**, 739 (1974); H. L. Yale and E. R. Spitzmiller, *ibid.*, **14**, 637 (1977).

(6) A number of 5-halogenated-2-pyridylenamines have previously been isolated in low yield from reactions between 2-amino-5-bromo-, 2-amino-5-chloro-, and 2-amino-5-iodopyridine and ethyl acetoacetate [V. F. Kucherov, *J. Gen. Chem. (U.S.S.R.)*, **20**, 1890 (1950); (*Chem. Abstr.*, **45**, 2951f (1951)]; *idem.*, *ibid.*, **21**, 1145 (1951); (*Chem. Abstr.*, **46**, 5043f (1952).] and from the reaction between 2-amino-3,5-dibromopyridine and ethyl acetoacetate [R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).]. That these earlier structural assignments were correct has now been confirmed by means of the pmr spectra of the 5-bromo-, 5-chloro- and 3,5-dibromo derivatives; all of these spectra show the diagnostic vinylic proton in the δ 4.70-4.90 region. See, also, H. Bohme and K. H. Wiesel, *Arch. Pharm.*, **309**, 966 (1976) and P. K. Kadaba, *J. Heterocyclic Chem.*, **13**, 1153 (1976).