Synthesis of Carbonyl Compounds via Biogenetic-Type Transamination Reaction

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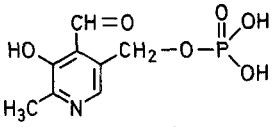
It is well-known that biochemical transamination is a mutual transformation between an α-amino acid and an α-keto carboxylic acid and that pyridoxal-5-phosphate (**1**) plays a very important role in the reaction[1].



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Several investigations on synthetic applications of the non-enzymatic reaction have been reported[2,3]; however, the methods are not easy to carry out because the used reagents such as 3,5-dinitromesitylglyoxal[2], 6-nitrobenzothiazole-2-carboxaldehyde[3], increasing of the equilibrium constant of the equilibrium:

are not easily available. Furthermore, no intermediates of the transamination have been isolated. The authors now present here a convenient procedure for a biogenetic-type transamination to prepare carbonyl compounds including several α-keto carboxylic acids from α-amino acids[4,5] by using commercially available isonicotinaldehyde (**3**).

We found that the Schiff base (**4**, $R^1 = C_6H_5$, $R^2 = H$), which was obtained from benzylamine (**2**) and isonicotinaldehyde (**3**), was smoothly converted to benzaldehyde (**7**) in quantitative yield by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol followed by acidic hydrolysis of the resulting intermediate **6**.

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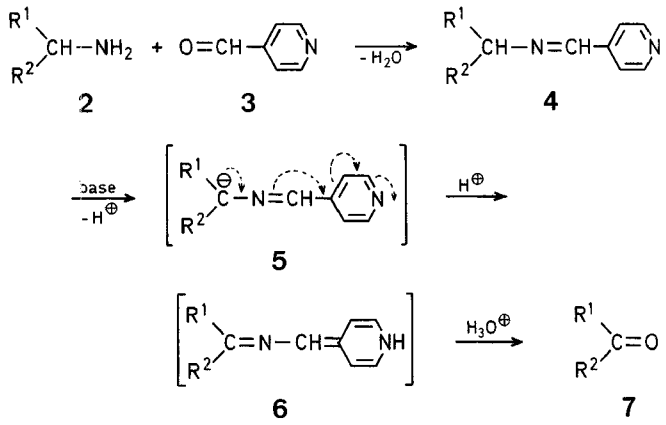


The Table shows several variations of the reaction conditions and their results. As shown in the Table, the new method was not only applicable to benzylic amines but also to cycloalkylamines, and several α-amino acids, however, the latter application seems to be difficult in the case of the preparation of easily water-soluble α-keto carboxylic acids[6].

In the case of 1,2,3,4-tetrahydronaphthylamine (run 8), a colorless crystalline intermediate [**6**; R^1, R^2: —(*o*-C_6H_4)—$(CH_2)_4$—] was isolated. In the case of *p*-nitrobenzylamine (run 6), the reaction mixture was treated with acetic anhydride to give a purple crystalline *N*-acetyl derivative of the intermediate (**6**; R^1 = *p*-nitrophenyl, R^2 = H). Hydrolyses of these intermediates in dilute hydrochloric acid/tetrahydrofuran gave the corresponding carbonyl compounds (α-tetralone in the former, and *p*-nitrobenzaldehyde in the latter) in reasonable yields.

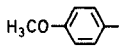
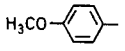
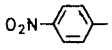
***p*-Chlorobenzaldehyde (Run 4); Typical Procedure:**

A mixture of *p*-chlorobenzylamine (1.70 g, 12 mmol) and isonicotinaldehyde (2.78 g, 26 mmol) is dissolved in dimethylformamide (24 ml), and DBU (1.83 g, 12 mmol) is added to the mixture, which is stirred overnight at room temperature. The mixture is acidified with 5% hydrochloric acid, extracted with ether (2 × 50 ml), the organic layer is washed with water (2 × 15 ml), and dried with sodium sulfate. Removal of the solvent gives almost pure *p*-chlorobenzaldehyde, yield: 1.40 g (83%), which is purified by vacuum distillation (Table).

α-Tetralone (Run 8); Typical Procedure:

DBU (1.83 g, 12 mmol) and sodium hydroxide (80 mg) are added to a solution consisting of 1-amino-1,2,3,4-tetrahydronaphthalene (1.77 g, 12 mmol), isonicotinaldehyde (1.54 g, 14 mmol), and methanol (24 ml) and the mixture is refluxed for 5 h. The reaction mixture is worked-up as described above to give almost pure α-tetralone; yield: 1.22 g (77%) (Table).

Table. Reaction Conditions and Yields of Carbonyl Compounds (**7**) Obtained

Run	R^1	R^2	Reaction Conditions Solvent/Time/Temp.[a]/Base (mmol)[b]	Yield [%] of 7[c,d]	m.p. [°C] or b.p. [°C]/torr	
					found	reported
1		H	CH_3OH/3 h/r.t./DBU (12)	100	175–176°/760	179°/760[7]
2		H	CH_3OH/3 h/r.t./DBU (12)	30	123–126°/12	89–90°/1.5[7]
3		H	DMF/15 h/r.t./DBU (12)	100		
4		H	CH_3OH/3 h/r.t./DBU (12)	83	42–46°	44–47°[8]
5		H	CH_3OH/3 h/r.t./DBU (12)	trace	104–106°	106–107°[7]
6			THF/3 h/r.t./$(C_2H_5)_3N$ (24)	40		
7			DMF/15 h/r.t./DBU (12)	100	107–108°/4	113–116°/6[8]
8			CH_3OH/5 h/reflux/DBU (12) + NaOH (80 mg)	77		
9	$-(CH_2)_5-$		CH_3OH/7 h/reflux/NaOH (80 mg)	79[e]	151–152°/760	155.6°/760[7]
10	$-(CH_2)_4-$		CH_3OH/7 h/reflux/NaOH (80 mg)	82[e]	128–130°/760	130.6°/760[7]
11		CH_3	DMF/15 h/r.t./DBU (12)	84	198–200°/760	202°/760[7]
12		COOH	DMF/5 h/r.t./DBU (24)	75	153–154° (dec.)	157° (dec.)[8]
13		COOH	DMF/5 h/r.t./DBU (24)	67	210–212° (dec.)	215° (dec.)[8]
14		COOH	DMF/5 h/r.t./DBU (24)	85	82–84°/15	84–85°/15[8]
15		COOH	DMF/5 h/r.t./DBU (24)	35	64–68°/12	65–67°/10[8]

[a] r.t. = room temperature (23–27 °C).
[b] Amount of base per 12 mmol of primary amine **2**.
[c] Products **7** characterized by I.R., ^{1}H-N.M.R., G.L.C. and/or m.p.; purity of oily products: >95% by G.L.C. (conditions: packing 3% SE-30, 2 m × Ø3 mm; N_2 30 ml/min; FID).
[d] Yield of isolated product.
[e] Yield by G.L.C.

Phenylpyruvic Acid (Run 12):
DBU (3.66 g, 24 mmol) is added to a suspension of L-phenylalanine (1.98 g, 12 mmol) in dimethylformamide (24 ml) containing isonicotinaldehyde (2.78 g, 26 mmol), and the mixture is stirred at room temperature for 5 h. The mixture is acidified with 5% hydrochloric acid and then extracted with ethyl acetate (2 × 50 ml), the organic phase is washed with water (2 × 15 ml), and dried with sodium sulfate. Removal of the solvent gives a crystalline residue, which is recrystallized from benzene; yield: 1.48 g (75%); m.p. 150–154 °C (dec.).

Indole-3-pyruvic Acid (Run 13):
DBU (3.66 g, 24 mmol) is added to a suspension of L-tryptophan (2.45 g, 12 mmol), the mixture is acidified with 5% hydrochloric acid, extracted with ethyl acetate (3 × 50 ml), the organic layer is washed with water (2 × 10 ml), and dried with sodium sulfate. Removal of the solvent gives an oily residue, to which is added water (0.5 ml) to precipitate a colorless solid. The solid is collected by suction, washed with cold water, and dried; yield: 1.77 g (67%). A pure sample is obtained by recrystallization from acetic acid; m.p. 210–214° (dec.).

Isolation of the Intermediate 6 [R^1-R^2: —(*o*-C_6H_4)—$(CH_2)_4$—]:
The Schiff base, derived from 1-amino-1,2,3,4-tetrahydronaphthalene (1.77 g, 12 mmol) and isonicotinaldehyde (1.29 g, 12 mmol), is refluxed in methanol (12 ml) in the presence of DBU (1.83 g, 12 mmol) and sodium hydroxide (80 mg) for 5 h under nitrogen. Ether (100 ml) and water (25 ml) are added to the mixture and the ethereal layer is washed with water (2 × 20 ml). A colorless crystalline powder is gradually precipitated from the ethereal solution, which is filtered, and dried; yield: 0.98 g (35%). Recrystallization from tetrahydrofuran/ether gives colorless needles; m.p. 214–216 °C.

M.S.: $m/e = 236.12675$ (M^+; calc. for $C_{16}H_{16}N_2$: 236.13135).

I.R. (KBr): $\nu = 1623$, 1595 cm^{-1} (C=N and C=C).

U.V. (C_2H_5OH): $\lambda_{max} = 213$ ($\log\varepsilon = 4.36$); 256 (4.24); 287 (3.54); 297 nm (3.40).

^{1}H-N.M.R. (DMSO-d_6/80 MHz): $\delta = 1.3$–1.8 (m, 2H); 2.1–2.75 (m, overlap with solvent signal); 5.20 (s, 1H, disappears on addition of D_2O); 6.95–7.45 (m, 6H); 8.0–8.2 (m, 1H); 8.35 ppm (dd, 2H, $J = 2$ Hz, 4 Hz).

Isolation of *N*-Acetylated Derivative of the Intermediate 6 (R^1 = *p*-nitrophenyl, R^2 = H):
A solution consisting of *p*-nitrobenzylamine (0.91 g, 6 mmol), isonicotinaldehyde (0.64 g, 6 mmol), triethylamine (1.21 g, 12 mmol), and anhydrous tetrahydrofuran (12 ml) is stirred for 1 h at room temperature under nitrogen. Acetic anhydride (0.62 g, 6 mmol) is added to the solution and the mixture is stirred for 2 h. The solvent is removed from the resulting mixture under reduced pressure, and methanol (10 ml) is added to the residue to precipitate purple fine leaflets; yield: 0.55 g (33%). Recrystallization from methanol gives deep purple leaflets: m.p. 150–156 °C (dec.).

$C_{15}H_{13}N_3O_3$	calc.	C 63.59	H 4.63	N 14.83
(283.2)	found	63.38	4.67	14.58

M.S.: $m/e = 283$ (M^+); 241 ($M^+ - CH_2{=}C{=}O$); 43 (100%).

I.R. (KBr): $\nu = 1665$ (C=O); 1650 (C=N, C=C); 1517 cm^{-1} (NO_2).

U.V. (C_2H_5OH): $\lambda_{max} = 263$ ($\log\varepsilon = 4.13$); 332 (4.18); 480 nm (3.62).

^{1}H-N.M.R. ($CDCl_3$/80 MHz): $\delta = 2.35$ (s, 3H); 5.90 (d, 1H, $J = 8$ Hz); 6.60 (s, 1H); 6.75–7.40 (m, 3H); 7.80 (d, 2H, $J = 9$ Hz); 8.00 (s, 1H); 8.20 ppm (d, 2H, $J = 9$ Hz).

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[3] V. Cálo, L. Lopez, P. E. Todesco, *J. Chem. Soc. Perkin Trans. 1* **1972**, 1652.
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[5] M. D. Broadhurst, D. J. Cram, *J. Am. Chem. Soc.* **96**, 581 (1974).
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[7] *The Merck Index* (9th Edition).
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