An Efficient Procedure for the Synthesis of *trans*-2-, -3-, and -4-Pyridalacetones

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The three isomeric pyridalacetones are potentially useful reagents in organic synthesis. In the course of our synthetic investigations, we required moderately large quantities of 2-, 3- and 4- *trans*-pyridalacetone **(5–7)** as starting materials. Although all three isomers have been prepared via base-catalyzed aldol condensations of acetone with each of the appropriate pyridinecarboxaldehydes or by means of a two-step preparation from the aldehydes and ethyl acetoacetate[1], all of the reported yields were less than 25% and in several instances the intermediate aldols did not readily undergo dehydration to the olefin.

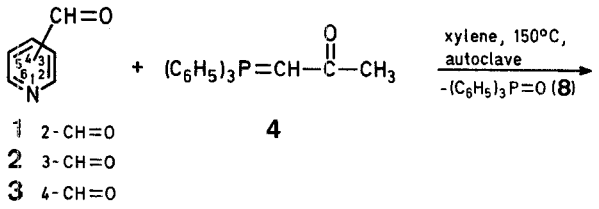
Table. *trans*-Pyridalacetones **5**, **6**, and **7**

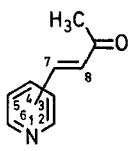
Product	Yield [%]		b.p. [°C]/torr		m.p. [°C] of picrate[a]	^{1}H-N.M.R. ($CDCl_3$/TMS)[b] δ [ppm]
	this method	Ref.[1]	found	Ref.[1]		
5	83	19	95–100°/0.3	59–59.5°/0.05	161–162°	2.40 (s, 3H); 7.15 (AB-q, J = 16 Hz, H-8); 7.28 (m, H-5); 7.49 (dd, J = 7.3 Hz, 0.5 Hz, H-3); 7.52 (AB-q, J = 16 Hz, H-7); 7.73 (m, H-4); 8.65 (dd, J = 4.0 Hz, 0.5 Hz, H-6)
6	87	12	106–110°/0.25	69.5–70°/0.05	168–169°	2.41 (s, 3H); 6.80 (d, J = 16.6 Hz, H-8); 7.36 (dd, J = 6.8 Hz, 5.9 Hz, H-5); 7.52 (d, J = 16.6 Hz, H-7); 7.88 (m, H-4); 8.62 (dd, J = 5.4 Hz, 0.4 Hz, H-6); 8.77 (d, J = 0.4 Hz, H-2)
7	76	21	108–110°/0.1	86–87°/0.07	178–179°	2.42 (s, 3H); 6.86 (d, J = 16 Hz, H-8); 7.41 (dd, J = 5.9 Hz, 0.4 Hz, H-3, H-5); 7.44 (d, J = 16 Hz, H-7); 8.66 (dd, J = 5.9 Hz, 0.4 Hz, H-2, H-6)

[a] Satisfactory N-analyses (±0.3) obtained.

[b] Measurements were made on a Nicolet NMC – 300 MHz NMR spectrometer using 8 μsec pulse width for 90° magnetization vector for ^{1}H nucleus with 5 sec delay time.

We describe here a general method for the synthesis of each isomer in satisfactory yield starting from the commercially available pyridine-2-, -3-, and -4-carboxaldehydes (**1–3**), triphenyl-(acetylmethyl)-phosphorane (**4**)[2] which are reacted in xylene solution in a stirring autoclave at elevated temperature. Examination of solvent and temperature conditions suggested the use of a sealed system in order to increase the reaction temperature in the solvent. A reaction time of 18 h is used in all of these preparations. The resulting compounds possess I.R. and U.V. spectra which are nearly identical with those reported[1] previously. Each isomer exhibits a characteristic *trans*-olefin band in the 970–980 cm^{-1} region. Compounds **5–7** can be characterized as picrates (Table).





5-7

In conclusion, the Wittig reaction between nitrogen-containing heterocylic carbonyl compounds and relatively unreactive, resonance-stabilized phosphoranes can be effectively carried out at elevated temperatures under an inert gas atmosphere such as is possible in a stirring autoclave. We have applied successfully these conditions to other syntheses with similarly unreactive systems.

***trans*-Pyridalacetones (5, 6, 7); General Procedure:**

A stirring autoclave of 300 ml capacity is successively charged with a pyridinecarboxaldehyde (**1–3**; 16.1 g, 0.15 mol), triphenyl-(acetylmethyl)-phosphorane (**4**; 47.7 g, 0.15 mol) and xylene (175 ml). The autoclave is then closed and purged with either nitrogen or hydrogen and is finally brought to a gas pressure of 100 psig. (6.8 atm). The vessel is stirred and maintained at 150 °C for 18 h. After cooling and venting, the contents are transferred using a small volume of benzene. The precipitated triphenylphosphine oxide (**8**) is collected on a filter and washed with additional benzene. The combined filtrates are then evaporated *in vacuo* to give a dark oil containing some solid **8**. This is diluted with ether (100 ml) and placed in the refrigerator for 18 h before collecting the additional precipitated **8** by filtration. Evaporation of the filtrate yields a dark oil which is distilled *in vacuo* to give the desired *trans*-pyridalacetone (**5–7**). The isolated **8** in these runs amounts to 75–80% of theory. In several preparations, it has been found that simple kugelrohr distillation at 0.05 torr gives products of suitable purity.

The picrates of **5**, **6** and **7** are prepared by adding a hot ethanol solution of picric acid to a solution of the base in the same solvent. After collection, the picrates are recrystallized from boiling ethanol/acetonitrile (1/1) and dried at 50 °C prior to analysis. All picrates are obtained as long yellow needles.

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[1] C.S. Marvel, J.K. Stille, *J. Org. Chem.* **22**, 1451 (1957).
[2] F. Ramirez, S. Dershowitz, *J. Org. Chem.* **22**, 44 (1957).