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An Improved and Practical Procedure for the Synthesis of Substituted Phenylacetylpyridines.

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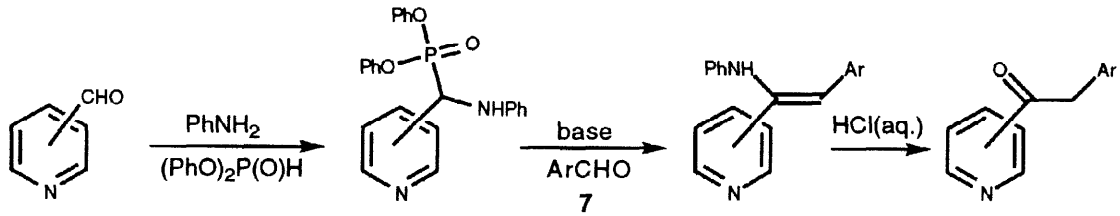
Abstract: *A general procedure for the synthesis of substituted phenylacetylpyridines in excellent yields is described using a Horner-Emmons condensation between α-aminoalkylphosphonates of pyridinecarboxaldehydes and benzaldehydes with cesium carbonate at room temperature.*

Phenylacetylpyridine derivatives **1-3** are important and common building blocks for drug candidates.[1] Of the methods used to prepare these compounds the *umpolung* property of an aldehyde derivative[2] is frequently employed. An attractive procedure for such a transformation using Horner-Emmons methodology was developed by Zimmer and Bercz (Scheme 1).[1b,d] Here, an aldehyde is converted to an *N,P*-acetal with aniline and diphenylphosphite. Coupling to a benzaldehyde using 10% methanolic KOH at -40 °C affords the enamine, which is hydrolyzed to the ketone. In our studies of this reaction we discovered the efficiency of this process was limited by the solvolysis/saponification of the phosphonate intermediate leading to unreactive byproducts. Herein, we wish to report a modification of this procedure using Cs_2CO_3 in THF/*i*-PrOH (IsoPropylAlcohol) that has overcome the shortcomings of this reaction.

Scheme 1



4a-c **5a-c** **6** **1-3**

In our study of the coupling of the *N,P*-acetal of pyridine-4-carboxaldehyde (**5c**)[3] and benzaldehyde (Scheme 1) only a 50% yield of the phenylacetylpyridine **3i** was obtained. A closer examination of the classical reaction conditions (KOH/MeOH) with 2-pyridyl *N,P*-acetal **5a** revealed by HPLC analysis[4] (Figure 1) that the substrate was readily decomposed within ten minutes at -40 °C after treatment with KOH. The byproducts were

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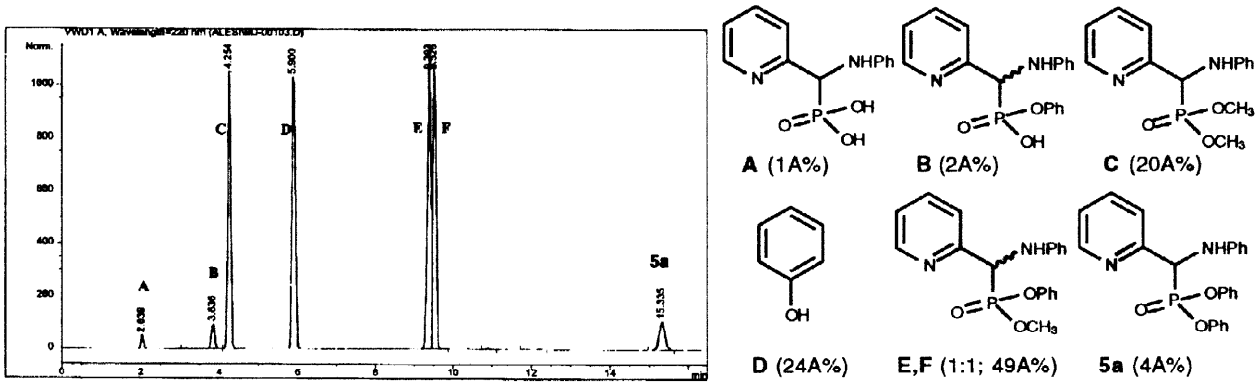
isolated and identified as **A-F**. These proved to be the result of saponification or solvolysis, liberating phenol (**D**). Apparently, the phosphonate is unstable to the reaction conditions. Therefore, in order to obtain effective, high-yielding couplings the phenylphosphonate must be kept intact.

Figure 1. Reverse-phase HPLC chromatogram of the degradates of 2-pyridyl *N,P*-acetal 5a after treatment with KOH/MeOH at -40 °C.



A survey of alternative bases[5] revealed that the milder base Cs_2CO_3 reduced considerably the degree of saponification and was more effective than hydroxides for the coupling reaction. The solvent choice also proved to be a key. No reaction occurred without a protic solvent. The less reactive *i*-PrOH limited the solvolysis of the *N,P*-acetal observed in methanol and ethanol. A 4:1 mixture of THF/*i*-PrOH at 0.6 M concentration gave the best results. Using 1.3 equiv of Cs_2CO_3 the reaction can be run at room temperature.[6] There is no need to preform the anion of the *N,P*-acetal. In fact, the yields are poorer if the benzaldehyde **7** is not present. By adding the Cs_2CO_3 to a mixture of the substrates in THF/*i*-PrOH the enamine **6** is formed within 16 hours. This intermediate is then converted directly to the ketone by addition of aqueous hydrochloric acid. This general procedure was applied to the three isomers of pyridinecarboxaldehyde **4a-c** and a variety of substituted benzaldehydes **7** (Scheme 2). Overall, the reaction is quite general for a variety of substrates affording the phenylacetylpyridines in >89% overall yield (Table). The position of the *N,P*-acetal on the pyridine ring does not affect its reactivity. Significantly, either electron-withdrawing or donating groups on the benzaldehyde can be tolerated.

Scheme 2

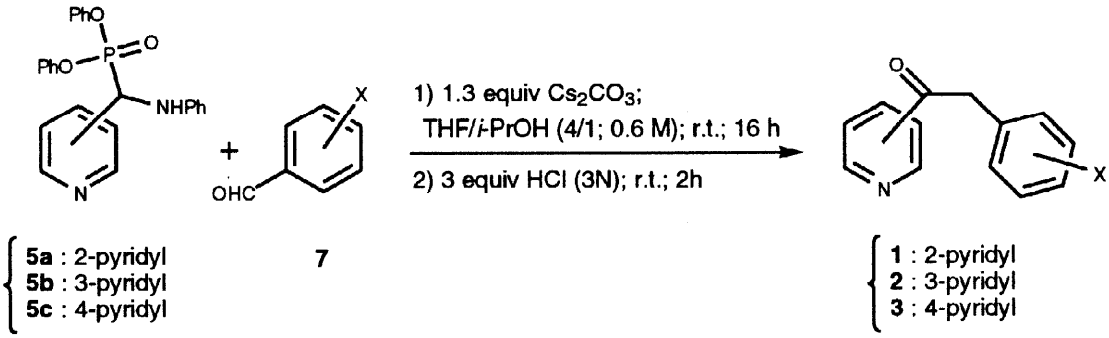


Table. Coupling of N,P-acetals 5 and Benzaldehydes 7 with Cs_2CO_3.

Ketone	X	Yield(%)[a]	Workup method[b]
1a	4-NO_2	93(c,d)	C
1b	3-NO_2	91	D
1c	4-CN	92	B
1d	4-Cl	90	D
1e	3-Cl	90	D
1f	4-Cl-3-NO_2	92	D
1g	4-CF_3	90	D
2a	4-NO_2	92	A
2b	3-NO_2	94	B
2c	4-CN	95	B
2d	4-Cl	91	B
2e	3-Cl	90	B
2f	4-Cl-3-NO_2	93(c)	C
2g	4-CF_3	91	B
2h	4-OCH_3	89(e)	D
2i	H	90	D
3a	4-NO_2	94	B
3b	3-NO_2	92(c)	C
3c	4-CN	96	B
3d	4-Cl	90	B
3e	3-Cl	91	B
3f	4-Cl-3-NO_2	93(c)	C
3g	4-CF_3	92	B
3h	4-OCH_3	91	D
3i	H	90	D

a) Isolated yield as free base unless otherwise indicated; b) see experimental; c) isolated as hydrochloride salt; d) the assay yield (determined by HPLC) was 98% (100% conversion) versus 83% assay yield (100% conversion) under Zimmer's conditions[1b] (KOH at -40 °C); e) Only 33% yield was obtained with Zimmer's conditions.

In conclusion, an improved procedure for the Horner-Emmons coupling to prepare phenylacetylpyridines has been developed. By using the combination of the mild base Cs_2CO_3 and the less reactive solvent *i*-PrOH, degradation of the phosphonate is avoided and high yields of the coupling are obtained.

General Experimental Procedure: The *N,P*-acetal (8.3 g, 20 mmol) and the benzaldehyde (22 mmol) were dissolved in a 4/1 mixture of THF/*i*-PrOH (50 mL). Anhydrous cesium carbonate (8.45 g, 26 mmol) was added in one portion and the reaction mixture was stirred for 16 hours at room temperature under nitrogen. The *N*-phenylenamine intermediate was hydrolyzed by the dropwise addition of 3N aqueous HCl (20 mL, 60 mmol). After ~2 hours at room temperature the product was isolated as follows: Method A: the reaction mixture was diluted with methyl *tert*-butylether (MTBE, 50 mL) and extracted with 1.2N HCl (4x40 mL). The combined aqueous layers were neutralized until pH 7-8 with 50% sodium hydroxide. The insoluble ketopyridine was filtered and washed with water (25 mL). The ketopyridine was recrystallized from EtOH/water. Method B: the reaction mixture was diluted with MTBE (50 mL) and extracted with 1.2N HCl (4x40 mL). The combined aqueous layers were neutralized until pH 7-8 with 50% sodium hydroxide and extracted with ethyl acetate (2X50 mL). The

organic layers were washed with brine (50 mL) and concentrated. The ketopyridine was crystallized from EtOH/water. Method C: the reaction mixture was diluted with MTBE (50 mL), cooled to 0 °C to crystallyze the product, which was filtered and washed with cold MTBE (25 mL) to give the benzylic ketopyridine as its hydrochloride salt. Method D: the reaction mixture was diluted with 5% aqueous NaOH (ca. 40 mL until pH 7-8) and extracted with ethyl acetate (2x50 mL). The combined organic layers were washed with brine (50 mL) and concentrated. The ketopyridine was chromatographed on silica gel using ethyl acetate/hexanes as the eluent.

References and notes:

(1) a) Burger, A.; Walter, C. R. *J. Am. Chem. Soc.* **1950**, *72*, 1988-1990. b) Zimmer, H.; Bercz, J. P. *Justus Liebigs Ann. Chem.* **1965**, *686*, 107-114. c) Bond, C. C.; Hooper, M. *Synthesis* **1974**, 443-443. d) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1988**, *110*, 4008-4017. e) Sheldrake, P.W. *Synth. Commun.* **1993**, *23*, 1967-1971. f) Pal, K.; Behnke, M. L.; Tong, L. *Tetrahedron Lett.* **1993**, *34*, 6205-6210. g) Katritzky, A. R.; Lang, H.; Wang, Z.; Zhang, Z.; Song, H. *J. Org. Chem.* **1995**, *60*, 7619-7624. h) Clader, J. W.; Berger, J. G.; Burrier, R. E.; Davis, H. R.; Domalski, M.; Dugar, S.; Kogan, T. P.; Salisbury, B.; Vaccaro, W. *J. Med. Chem.* **1995**, *38*, 1600-1607.

(2) For reviews, see ref. 1g.

(3) The *N,P*-acetals **5a-c** were prepared by mixing the respective pyridinecarboxaldehyde **4a-c** with aniline (1.2 equiv) and diphenylphosphite (1.6 equiv) in a variety of solvents, such as ethanol, *i*-PrOH, isopropyl acetate, methyl *tert*-butylether, or acetonitrile. Isopropyl alcohol was preferable and allowed a good recovery of product. Attempts at using the crude *N,P*-acetal without isolation by adding the base directly failed to give good quality product. A general procedure for the *N,P*-acetal follows: 3-pyridinecarboxaldehyde (**4b**) (32.1 g, 0.3 mole) was dissolved in 650 mL of *i*-PrOH and stirred at room temperature. Aniline (32.8 mL, 0.36 mole) was added in one portion followed by the addition of diphenylphosphite (102 mL of 85-90 wt%, ca. 0.48 mole) in one portion. The temperature gradually raised to 35 °C over 15 minutes and the *N,P*-acetal started to crystallize after 30-45 minutes. The slurry was aged for 4 hours at room temperature, cooled to 0 °C, filtered and washed with 100 mL of cold *i*-PrOH to give 107 g of a white solid (86% yield, >99% purity).
The same procedure gave the 2-pyridyl isomer **5a** (precipitated as a thick heavy white solid) in 88% yield (110 g; >99% purity).
The 4-pyridyl isomer **5c** was prepared in a 4/1 mixture of MTBE/*i*-PrOH to give 103.5 g of a pale yellow solid (83% yield; >99% purity).

(4) HPLC conditions for the 3- and 4-pyridyl *N,P*-acetal (**5b** and **5c**): HP 1050, Metachem inertsil ODS-3 column (250x4.6 mm); 1.5 mL/min; detection at 220 nm. A: H_2O (0.1% $HClO_4$), B: acetonitrile; gradient elution: 85% A at 0.0 min., 65% A at 10.0 min., 30% A at 20.0 min; **5b**, 16.75 min.; **5c**, 16.25 min. The HPLC conditions for the 2-pyridyl N,P-acetal **5a** : 70% A at 0.0 min., 40% A at 10.0 min.; **5a**, 15.35 min.

(5) Other bases tested were *n*-butyllithium in THF, DBU, potassium *tert*-butoxide, and NaOH.

(6) Anhydrous conditions (KF≤110μg H_2O/mL) were crucial in preventing the formation of the unreactive monosaponified phosphonate. Cesium carbonate was dried at 150 °C under vacuum (~1 mm Hg) for 16 h.