Synthesis of Functionalized 3-Pyridyl Methyl Ketones

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A synthesis of 3-pyridyl methyl ketones is described that employs a palladium-catalyzed olefination of 3-bromopyridines with butyl vinyl ether followed by acid hydrolysis of the intermediate pyridyl vinyl ether *in situ*. This method has been applied to bromoquinoline substrates as well. The reaction is compatible with a variety of functional groups.

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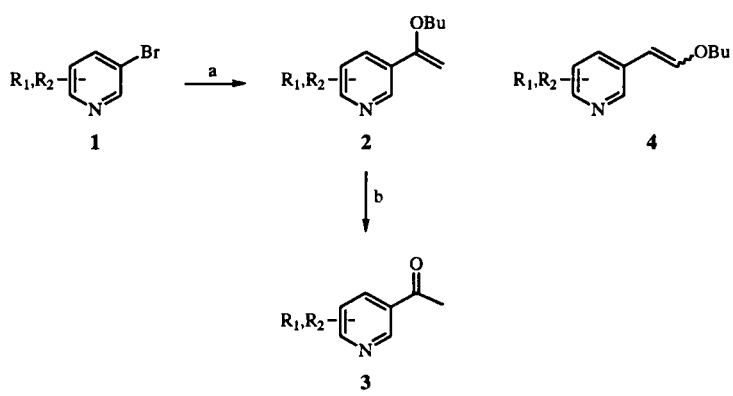
Functionalized 3-pyridyl ketones have been a relatively inaccessible class of compounds, with few synthetic approaches to functionalized 3-pyridyl ketones reported in the literature. The syntheses that have been published generally require that the corresponding pyridine 3-carboxylic acid be prepared for use as a starting material, and proceed from the pyridine 3-carboxylic acid or a derivative *via* the use of polar organometallic reagents such as organolithium or Grignard reagents [1]. Other methods that have been reported include the oxidation of indole derivatives [2], the hydration of 3-alkynyl pyridines [3], and the carbonylation of 3-bromopyridines by dicobalt octacarbonyl [4]. All of these methods have their disadvantages, including multistep reaction sequences, low overall yields, and the use of relatively inaccessible starting materials.

Scheme 1



1 2 4 3

(a) *n*-BuOCH=CH$_2$, Pd(OAc)$_2$, (*o*-tolyl)$_3$P, Et$_3$N, CH$_3$CN, 80°; (b) HCl, H$_2$O, 20°

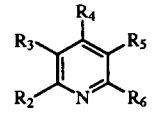
An alternative route to 3-pyridyl ketones that circumvents many of these difficulties is outlined in Scheme 1, which employs 3-bromopyridines **1** in a palladium-catalyzed Heck-type olefinic coupling with a vinyl ether [5] to afford 1-(3-pyridyl)-1-alkoxyalkenes **2**, which upon acid hydrolysis furnishes the 3-pyridyl ketones **3**. This procedure offers several advantages over those previously used for the synthesis of 3-pyridyl ketones, including mild reaction conditions that are tolerant of nearly all functional groups, a two-step, one-pot reaction, and reasonable yields. Most importantly, the necessary 3-bromopyridines are well known compounds that are readily available in good yields by a variety of methods, including functional group interchange [6], directed metalation [7], and directed electrophilic bromination of the pyridine ring [8]. In as much as Heck-type olefination reactions with vinyl ethers can afford a mixture of vinyl ether regioisomers **2** and **4**, the success of this approach depended critically upon the regiochemical outcome of the olefination reaction. However, literature precedent [9] suggested that, with an electron rich aryl bromide and the use of phosphine ligands in a coordinating solvent, the olefination should proceed with the formation of the desired vinyl ether **2** as the dominant product. Despite the fact that pyridines are generally accepted to be electron-deficient arenes, we reasoned that relatively electron-rich pyridines, such as aminopyridines and alkoxypyridines, which are sufficiently electron-rich to be capable of undergoing uncatalyzed ring halogenation, should be suitable substrates for this transformation.

In a typical experiment, the 3-bromopyridine substrate **1** was treated with 2 equivalents of butyl vinyl ether, 0.08 equivalents of palladium acetate, 0.16 equivalents of tri-*o*-tolylphosphine, and 1.6 equivalents of triethylamine in acetonitrile under reflux until the 3-bromopyridine was consumed as judged by tlc or gc analysis of the reaction

mixture. The reaction mixture was then concentrated to dryness. Analysis (gc-ms) of the crude product at this point indicated the presence of all three isomeric enol ether products: **2** and the *E*- and *Z*- isomers of **4**, with **2** being the predominant component in most cases. The residue was dissolved in 6 *M* hydrochloric acid for a short time, typically 15 minutes, which was sufficient to hydrolyse the vinyl ether intermediate **2** without effecting significant hydrolysis of the regioisomeric vinyl ether by-products **4**. The product was purified by chromatography and subsequently recrystallized or distilled.

higher yield of ketone (60%). The results obtained with **1k**, **1l**, **1m**, **1n**, and **1p** suggest that the desired vinyl ether olefination reaction becomes inoperative with the most electron deficient pyridines, and that this trend can be reversed by the addition of suitable electron releasing substituents as in **1o**. Not surprisingly, 2-bromopyridines and 4-bromopyridines were unreactive under these conditions [10]. Attempts to substitute a vinyl ester for the vinyl ether component of the reaction mixture were likewise unsuccessful [11]. Tri-*o*-tolylphosphine was found to afford significantly improved yields with **1a**; by comparison, an equivalent quantity of triphenylphosphine instead of tri-*o*-tolylphosphine with **1a** under the same conditions afforded only a 41% yield of **3a**, along with much dark colored tarry material.

Table 1



Bromide	R_2	R_3	R_4	R_5	R_6	Product	R_2	R_3	R_4	R_5	R_6	Yield of **3** [a]	mp of **3**, °C
1a [b]	AcNH	H	H	Br	H	**3a**	AcNH	H	H	MeCO	H	65%	146-147
1b [c]	Me_3CCONH	H	H	Br	H	**3b**	Me_3CCONH	H	H	MeCO	H	80%	113-115
1c	AcNH	H	H	Br	Me	**3c**	AcNH	H	H	MeCO	Me	96%	192-193
1d	AcNAc	Br	H	Me	H	**3d**	AcNH	MeCO	H	Me	H	52%	93-94
1e	AcNAc	Me	H	Br	H	**3e**	AcNH	Me	H	MeCO	H	40%	115-116
1f [d]	AcNH	H	Me	Br	Me	**3f**	AcNH	H	Me	MeCO	Me	90%	150-151
1g [e]	MeO	H	H	Br	H	**3g**	MeO	H	H	MeCO	H	87%	52-53
1h [f]	H	Br	H	H	H	**3h**	H	MeCO	H	H	H	70%	oil
1i [g]	-CH=CH-CH=CH-		H	Br	H	**3i**	-CH=CH-CH=CH-		H	MeCO	H	60%	94-95
1j	$C_6H_5CH_2OCONH$	H	H	Br	H	**3j**	$C_6H_5CH_2OCONH$	H	H	MeCO	H	66%	186 dec
1k	CF_3CONH	H	H	Br	H	**3k**	CF_3CONH	H	H	MeCO	H	---	no reaction
1l	TsNH	H	H	Br	H	**3l**	TsNH	H	H	MeCO	H	---	no reaction
1m	H	CO_2Et	H	Br	H	**3m**	H	CO_2Et	H	MeCO	H	13%	124-126
1n	(Succinimide)N	H	H	Br	H	**3n**	(Succinimide)N	H	H	MeCO	H	70%	137-140
1o	MeO	CO_2Et	H	Br	H	**3o**	MeO	CO_2Et	H	Br	H	60%	81-83
1p	CF_3CONMe	H	H	Br	H	**3p**	CF_3CONMe	H	H	MeCO	H	---	no reaction

[a] All yields refer to chromatographed and subsequently recrystallized or distilled products. [b] E. Placek and E. Sucharda, *Ber.*, **61**, 1813 (1928). [c] T. R. Kelly, C. T. Jagoe and Z. Gu, *Tetrahedron Letters*, **32**, 4263 (1991). [d] R. P. Mariella and E. P. Belcher, *J. Am. Chem. Soc.*, **74**, 1916 (1952). [e] D. L. Comins and M. L. Killpack, *J. Org. Chem.*, **55**, 69 (1990). [f] Aldrich Chemical. [g] 3-Bromoquinoline (Aldrich Chemical).

The reaction proved to be generally successful for most of the substrate bromopyridines examined, including even such unactivated bromides such as 3-bromopyridine (Table 1). The reaction was compatible with a number of functional groups, including the amine protecting groups *N*-acetyl **1a**, *N*-pivaloyl **1b**, and *N*-benzyloxycarbonyl **1j**, as well as an ether group **1g**, and ester groups, **1m**, **1o**. The reaction was also successful for the unsubstituted pyridine **1h** and quinoline **1i**. The acyclic imides **1d** and **1e** underwent cleavage during the course of the reaction and workup to afford the amides **3d** and **3e**, while the cyclic imide **1n** survived these conditions. No reaction was observed with the trifluoroacetamides **1k** and **1p**, or the *p*-toluenesulfonamide **1l**, which were recovered unchanged in high yield. Ethyl 5-bromonicotinate (**1m**) afforded a low yield of ketone (13%), while ethyl 2-methoxy-5-bromonicotinate (**1o**) gave a four-fold

The vinyl ether intermediate **2** could be isolated from the reaction mixture if the olefination reaction mixture was concentrated and chromatographed instead of being treated with aqueous acid. Not surprisingly, the vinyl ethers **2** were extremely labile, undergoing both cleavage to the ketones **3** and polymerization.

EXPERIMENTAL

All reactions were carried under an atmosphere of dry nitrogen. All solutions were dried over anhydrous magnesium sulfate; all evaporations were carried out on a rotary evaporator at