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ONE-POT SYNTHESIS OF FURAN SYSTEMS BEARING 2-PYRIDYL SUBSTITUENT

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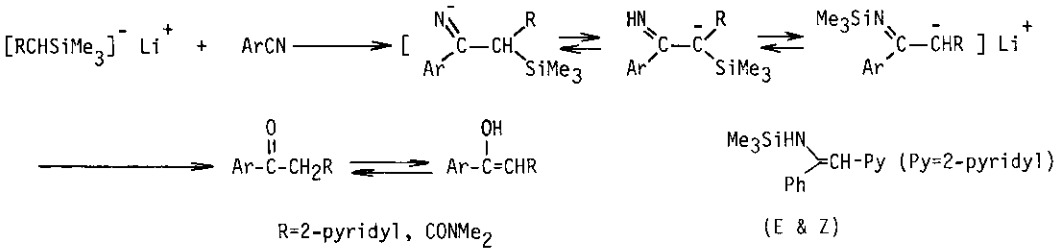
Abstract —— The reaction of an anionic intermediate, generated in situ from the lithio derivative of 2-(trimethylsilylmethyl)pyridine and an aromatic nitrile, with α-haloketones such as phenacyl bromide, desyl chloride and 2-bromocyclohexanone provided a route to a one-pot synthesis of rare 2-pyridyl substituted furans. The reaction pathway is also described.

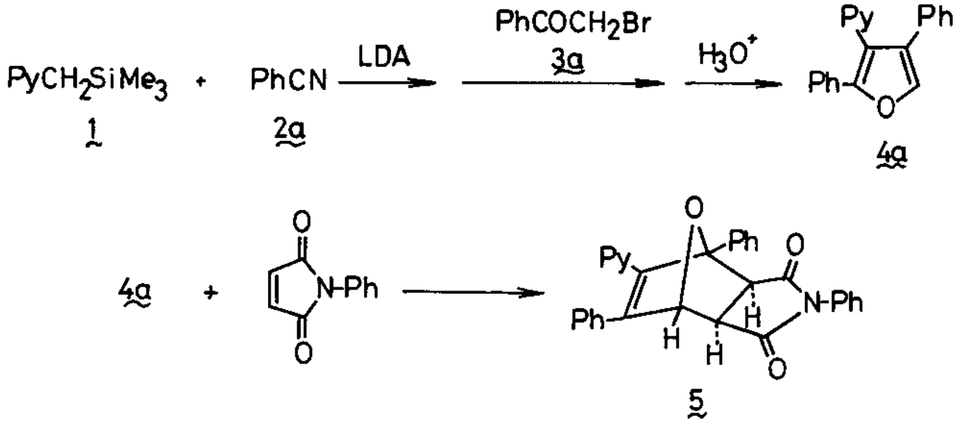
Recently, it has been demonstrated that the reaction of lithio derivatives of 2-(trimethylsilylmethyl)pyridine and N,N-dimethyltrimethylsilylacetamide with aromatic nitriles provided a prominent route to the corresponding ketones[1,2]. The above reaction certainly proceeds via an intermediate which is represented as tautomeric anions, because from the reaction of lithio derivative of 2-(trimethylsilylmethyl)pyridine with benzonitrile a mixture of (E)- and (Z)-1-phenyl-2-(2-pyridyl)-1-trimethylsilylaminoethene (4:1) was isolated in a quantitative yield[2] (Scheme 1).



Scheme 1

The anionic intermediate might be expected to further react with an electrophile. In this paper we report the reaction of the anionic intermediate, generated in situ from the lithio derivative of 2-(trimethylsilylmethyl)pyridine (**1**) and aromatic nitrile (**2**), with α-haloketones: It is noteworthy that the reaction provides a one-pot synthesis of rare pyridylfurans.

A typical run is illustrated by the reaction of the anionic intermediate, generated from lithio derivative of the silyl compound 1 and benzonitrile (2a), with phenacyl bromide (3a). A solution of 1 (0.495 g, 3.0 mmol) in THF (5 ml) was added to a THF solution of lithium diisopropylamide (LDA), prepared from a 15% solution of butyllithium in hexane (2.25 ml, 3.6 mmol) and diisopropylamine (0.382 g, 3.6 mmol) in THF (10 ml), at - 78°C with stirring under oxygen-free dry nitrogen. To the solution, a solution of benzonitrile (2a) (0.309 g, 3.0 mmol) in THF (5 ml) was added dropwise over 5 min. The resultant mixture was allowed to warm to room temperature with stirring during 1 h, and then stirred for an additional 1 h at room temperature. A solution of the bromide 3a (0.537 g, 2.7 mmol) in THF (5 ml) was added to the above mixture at room temperature, and the mixture was refluxed for 3 h. After it had been cooled, the reaction mixture was stirred with conc. hydrochloric acid (2 ml) for 20 min, poured into water (100 ml), and then completely extracted with ether. The extract was dried over $MgSO_4$, and evaporated in vacuo to leave a residue which purified by chromatography on silica gel to give 0.573 g (71%) of 2,4-diphenyl-3-(2-pyridyl)furan (4a), mp 114-116°C, as colorless prisms. Structural elucidation of 4a was accomplished on the basis of spectral data[3] as well as chemical conversion. The furan 4a reacted with N-phenylmaleimide in refluxing benzene to give the exo-Diels-Alder adduct 5, mp 150-152°C, in 31% yield[4] (Scheme 2).

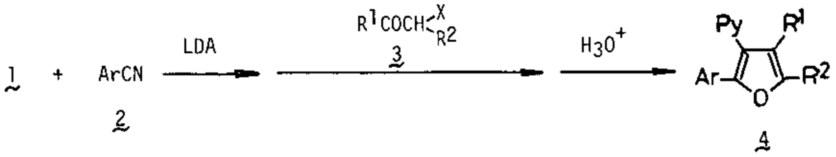


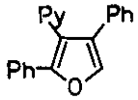
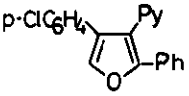
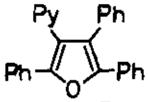
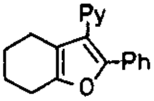
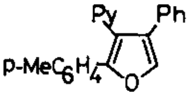
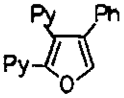
Py=2-pyridyl

Scheme 2

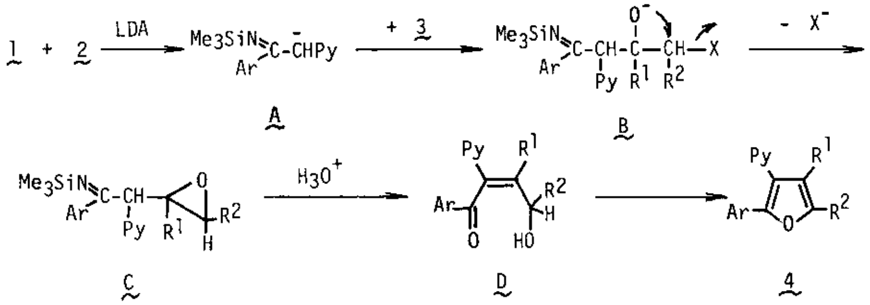
Similarly, one-pot synthesis of furans was performed by the reaction of anionic intermediates, generated from the lithio derivative of 1 and aromatic nitriles, with phenacyl bromide (3a), p-chlorophenacyl bromide (3b), desyl chloride (3c) and/or 2-bromocyclohexanone (3d). The results are summarized in Table I. Structural elucidation of the furans 4b—4f was again accomplished on the basis of their spectral data[5].

Table I. One-pot Synthesis of Furans



2		3				4		
	Ar		R^1	R^2	X			Yield, %
2a	Ph	3a	Ph	H	Br	4a		71
2a	Ph	3b	p-ClC_6H_4	H	Br	4b		40
2a	Ph	3c	Ph	Ph	Cl	4c		58
2a	Ph	3d	-$(CH_2)_4$-		Br	4d		28
2b	p-tolyl	3a	Ph	H	Br	4e		38
2c	Py	3a	Ph	H	Br	4f		37

Although a few pyridyl-substituted furans (furylpyridines) have been prepared[6], our one-pot procedure is superior to the reported methods because of possible choice of substituents involved in the 1-, 3- or 5-position of furans.



Py=2-pyridyl

Scheme 3

The pathway for the formation of furans **4** is outlined in Scheme 3. An anionic intermediate, e.g. **A**, generated from **1** and **2** in the presence of LDA, attacks on the carbonyl carbon in α-haloketone **3** to yield **B**, and then by an intramolecular nucleophilic substitution **B** forms an oxirane intermediate **C**. On treatment with hydrochloric acid **C** is converted into furan **4** through **D**. Although attempts to isolate **C** were unsuccessful in all runs, a few examples of furan synthesis from oxiranes have been reported[7].

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2. O. Tsuge, K. Matsuda, and S. Kanemasa, *The Reports of Research Institute of Industrial Science, Kyushu University*, 1983, No. 74 in press.

3. All new compounds gave satisfactory elemental analyses. **4a**: Ir (KBr) 1595 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 6.90-7.50 (13H, m), 7.62 (1H, s, α-H of furan ring), 8.60-8.70 (1H, m, α-H of pyridine ring); mass spectrum m/e 297 (M$^+$).

4. **5**: Ir (KBr) 1775, 1705 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.51, 4.12 (each 1H, d, J=7.0 Hz), 5.87 (1H, s), 7.00-7.50 (18H, m); mass spectrum m/e 297, 173.

5. **4b**: Mp 124-125°C; ir (KBr) 1590 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 6.90-7.60 (12H, m), 7.54 (1H, s, α-H of furan ring), 8.50-8.70 (1H, m); ^{13}C nmr ($CDCl_3$) δ 138.6 (d, 5-C), 151.4 (s, 2-C); mass spectrum m/e 332, 330 (M$^+$). **4c**: Mp 184-185°C; ir (KBr) 1595, 1585 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 6.90-7.60 (18H, m), 8.40-8.60 (1H, m); ^{13}C nmr ($CDCl_3$) δ 147.7, 148.9 (each s, 2- and 5-C); mass spectrum m/e 373 (M$^+$). **4d**: Mp 114-116°C; ir (KBr) 1585 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.50-2.00 (4H, m), 2.20-2.80 (4H, m), 6.90-7.60 (8H, m), 8.50-8.70 (1H, m); mass spectrum m/e 275 (M$^+$). **4e**: Mp 146-148°C; ir (KBr) 1600, 1580 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.17 (3H, s), 6.80-7.60 (17H, m), 8.40-8.60 (1H, m); mass spectrum m/e 387 (M$^+$). **4f**: Mp 124-125°C; ir (KBr) 1585 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 6.90-7.60 (11H, m), 7.66 (1H, s, α-H of furan ring), 8.40-8.70 (2H, m); mass spectrum m/e 298 (M$^+$).

6. For example, R. Faragher and T. Gilchrist, *J. C. S. Chem. Comm.*, 1977, 252; K. T. Potts, M. J. Cipullo, P. Ralli, and G. Theodoridis, *J. Am. Chem. Soc.*, 1981, **103**, 3584; L. Fišera, J. Kováč, and E. Komanová, Tetrahedron, 1974, **30**, 4123.

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