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FORMATION AND REACTIVITY OF DILITHIATED N-FURFURYLBENZAMIDES. SYNTHESIS OF α-SUBSTITUTED N-FURFURYLBENZAMIDES

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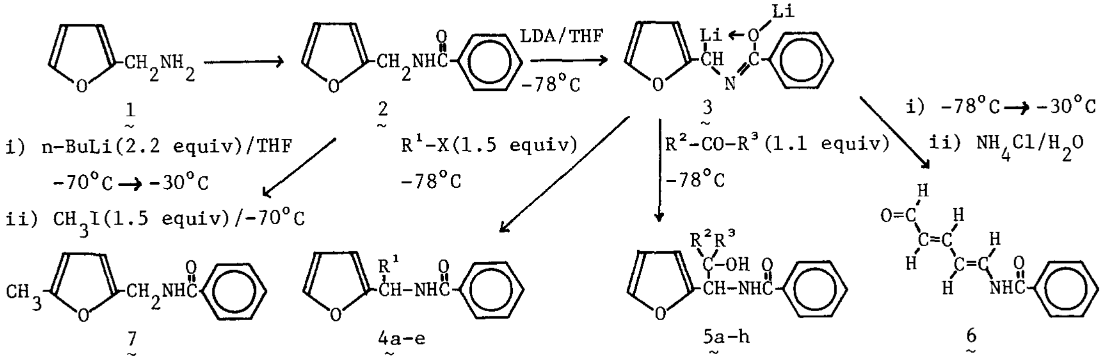
Summary : Dianion 3 can be efficiently and regioselectively generated from N-furfurylbenzamide with lithium diisopropylamide/tetrahydrofuran/-78°C and react with various electrophiles to give α-substituted N-furfurylbenzamide derivatives in good yields.

It is well known that direct lithiation of a furan nucleus with strong base occurs exclusively at the α-position to oxygen[1]. However, it has been recently reported that treatment of a furan derivative having an anion stabilizing group(1,3-dithiane[2], phenyl or trimethylsilyl[3]) at the furfuryl position with n-BuLi results in the formation of the furfuryl carbanion. In this report we wish to describe a new approach to the synthesis of α-substituted N-furfurylbenzamides via an α-carbanion of the furfurylamine derivative 2. N-Furfurylbenzamide 2, obtained by benzoylation of furfurylamine(1), undergoes efficient and regioselective lithiation on reaction with lithium diisopropylamide(LDA)(2.5 -3.0 equiv)/tetrahydrofuran(THF)/-78°C to give dianionic species 3, which reacts readily with various electrophiles(alkyl halides, aldehydes, ketones, and carbon dioxide)(1.1 - 1.5 equiv) to yield α-substituted furfurylbenzamide derivatives 4 and 5. The results for the reaction with alkyl halides(R^1-X) and carbonyl compounds(R^2-CO-R^3) as electrophile are listed in Table 1.



α-Alkylated N-furfurylbenzamides 4a-c have been proved to be a good intermediate to N-benzoyl α-amino acids via oxidative cleavage of the furan ring using a $KMnO_4$/KOH/acetone system[4]. The previous reported procedure[4] for the preparation of α-alkylated N-furfurylbenzamides required the tedious several steps. Therefore, the present method for the general synthesis of α-substituted N-furfurylbenzamides 4a-e would provide a novel synthetic route to α-amino acids from furfurylamine(1). β-Hydroxy amino derivatives 5 having furyl group at α-position are of particular interest as they may be related to adrenergic amines in their structure and pharmacological properties, and also as versatile intermediates in organic synthesis.

Furthermore, the temperature dependent rearrangement of the dianion 3 was examined. The dianion 3(intense blue colour) underwent a facile ring opening reaction[5] when warmed to -30°C

Table 1

Reaction of Dianion 3 with Alkyl Halides(R^1-X) and Carbonyl Compounds(R^2-CO-R^3)

Entry	Electrophiles	Products	Yield(% isolated)
1	methyl iodide	(4a) ($R^1 = CH_3$)	67
2	n-butyl iodide	(4b) ($R^1 = n\text{-}C_4H_9$)	65
3	iso-propyl iodide	(4c) ($R^1 = iso\text{-}C_3H_7$)	21
4	allyl bromide	(4d) ($R^1 = CH_2CH{=}CH_2$)	57
5	benzyl bromide	(4e) ($R^1 = CH_2C_6H_5$)	69
6	benzaldehyde	(5a) ($R^2 = H$, $R^3 = C_6H_5$)	70
7	anisaldehyde	(5b) ($R^2 = H$, $R^3 =$ 4-methoxy-C_6H_4)	85
8	veratraldehyde	(5c) ($R^2 = H$, $R^3 =$ 3,4-dimethoxy-C_6H_3)	75
9	piperonal	(5d) ($R^2 = H$, $R^3 =$ 3,4-methylenedioxy-C_6H_3)	76
10	acetophenone	(5e) ($R^2 = CH_3$, $R^3 = C_6H_5$)	63
11	benzophenone	(5f) ($R^2 = R^3 = C_6H_5$)	72
12	cyclopentanone	(5g) ($R^2 =(CH_2)_4= R^3$)	87
13	carbon dioxide	(5h) ($R^2 = O = R^3$)	70

to form the brown solution. The reaction mixture was quenched with aq. sat. NH_4Cl solution to furnish all-trans-5-benzamide-2,4-pentadienal(6) in 95 % yield. The structural and stereochemical assignment to 6 was made on the basis of spectral data(IR, ^{1}H-NMR, ^{13}C-NMR, Mass) in comparison with that of the Zincke aldehyde[6]. On the other hand, in using of n-BuLi(2.2 equiv)/THF/ -70°C system, then warming to -30°C instead of LDA system as mentioned above, 2 underwent direct lithiation at 5-position of furan ring, followed by reaction with methyl iodide at -70°C to give 5-methylated furan derivative 7 in 66 % yield accompanying with 6(18%) and 4a(trace). In this reaction any methylated products formed from the corresponding ortho-lithiated dianion(3-furyl and/or 2-phenl) were not obtained[7].

All new compounds reported here gave satisfactory elemental analysis. Their IR, NMR, and Mass spectra are in agreement with the proposed structures. Further studies of the scope and limitation of these related reactions are currently in progress[8].

References and Footnotes

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