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Annulation of Functionalized Hexadienones as An Efficient Regioselective Approach to N-Aryl-2-(trifluoromethyl)-4-pyridinamines

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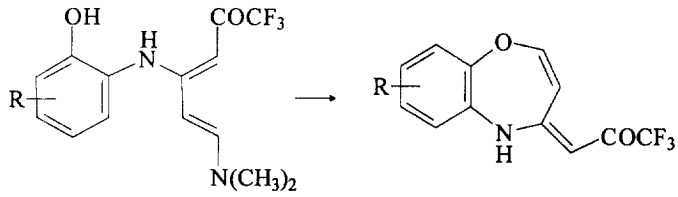
Abstract: Readily accessible fluorinated N-arylenaminones **3** were reacted with N,N-dimethylformamide dimethylacetal to produce functionalized hexadienones **4**. Ring closure of **4** with ammonium acetate afforded selectively N-aryl-2-(trifluoromethyl)-4-pyridinamines **5** in good to excellent yields.

Keywords: Dienones, annulation, pyridines, regioselection.

N-Aryl-4-pyridinamines have recently acquired great importance as adrenergic agents,[1] CNS drugs,[2] antihypertensives[3] and anticonvulsant agents,[4] while the diuretic Torasemide and the cardiovascular agent MCI-154 have shown useful clinical activities.[5] Introduction of a trifluoromethyl group into bioactive molecules sometimes results in significant enhancement, not only of the potency, but also of the duration of action because of increased lipophilicity:[6] development of efficient methodologies for the synthesis of trifluoromethylated analogues has attracted great attention.[7] Synthetic procedures for access to N-aryl-4-pyridinamines involve the reaction of arylamines with 4-chloropyridine[8] or its hydrochloride[9] or with 4-chloro-1-pyridiniopyridinium salts[10] or the reaction of an active aryl chloride with 4-aminopyridine.[11] Nevertheless, these methods require vigorous reaction conditions and do not always give satisfactory yields. On the other hand, direct trifluoromethylation[12] and the construction of trifluoromethylated precursors[13] are widely employed for the synthesis of trifluoromethylated organic compounds. Previously,[14] we have been interested in the regioselective synthesis of (trifluoromethyl)pyridines by reacting enamines with trifluoroacetylvinyl ethers; moreover[15] we have developed a synthetic pathway for the introduction of the trifluoromethyl moiety into 1,5-benzoxazepine derivatives by involvement of trifluorinated hexadienones as key intermediates.



As an extension of our study on the synthetic potential of functionalized dienones, we are now interested in the annulation of a series of 4-(arylamino)-1,1,1-trifluoro-3,5-hexadienones **4** as a general synthetic procedure for regioselective access to N-aryl-2-(trifluoromethyl)-4-pyridinamine derivatives **5**. Preliminary results are report herein.

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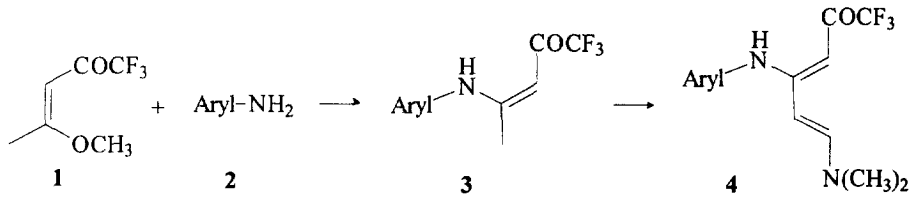
A pathway for the preparation of hexadienones **4** is outlined in Scheme 1. Equimolecular amounts of the enol ether **1** and arylamines **2** were reacted at reflux in dry MeCN to give enaminones **3** in 64 to 96 % yields. By a slight modification of the reported[15] procedure, reaction of compounds **3** with DMF-DMA, in a 1:4 molar ratio in boiling benzene or toluene, selectively produced 6-(dimethylamino)-(3Z, 5*E*)-4,6-hexadienones **4**[16] in 60 to 97 % yields.

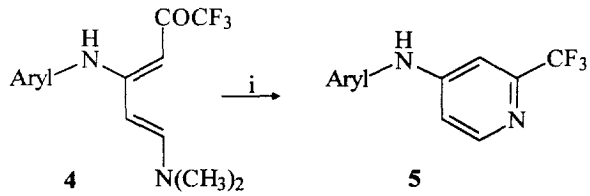


1 2 3 4

Scheme 1

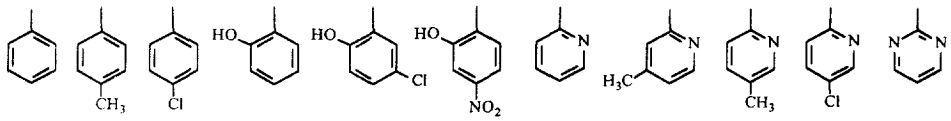
Hexadienones **4** readily cyclize with ammonium acetate to give 4-(arylamino)-2-(trifluoromethyl)pyridine derivatives **5** selectively in good to excellent yields (Table 1).

Table 1: Synthesis of N-Aryl-2-(trifluoromethyl)-4-pyridinamines



4 5

i) NH_4OAc (2 equiv.)/DMF, reflux 2 hours.

Entry	1	2	3	4	5	6	7	8	9	10	11
Aryl											
Yield (%)[a]	89	82	85	75	81	73	84	68	85	98	76

[a]) Isolated yield

Among other methods (NH_4OH/ethanol[17] or MeCN, [18] NH_4OH or NH_4OAc/THF, [19] NH_4OAc/DMF[20]) utilized by us to achieve pyridine ring closure, the best results were obtained by reacting compound **4** with two equivalents of ammonium acetate for two hours in boiling DMF solution. The structures of compounds **5** were confirmed by microanalyses, IR and ^1H NMR spectral data.[21]

In summary, easily available starting materials and efficient formation of N-aryl-4-pyridinamine derivatives make this method very attractive and suitable for further applications.

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16. Typical spectral data for compound **4**: (*3Z,5E*)-6-(dimethylamino)-1,1,1-trifluoro-4-(phenylamino)-3,5-hexadien-2-one; IR (Nujol): 1630, 1595, 1590 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/TMS): δ 2.64 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 4.87 (d, J = 12.5 Hz, 1H, H-5), 5.68 (s, 1H, H-3), 7.10-7.39 (m, five phenyl Hs), 7.85 (d, J = 12.5 Hz, 1H, H-6), 12.70 (brs, 1H, NH, D_2O exchangeable).

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21. Typical spectral data for compound **5** (Entry 1): IR (Nujol) 3240, 3160, 3080, 1615, 1590 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/TMS): δ 7.02 (d, J = 5.9 Hz, 1H, H-5), 7.06-7.36 (m, 6H, five phenyl Hs and H-3), 8.24 (d, J = 5.9 Hz, 1H, H-6), 9.20 (s, 1H, NH, D_2O exchangeable).