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Solvent Free Aza-annulation using 4-Dimethylamino 2-Aza-1,3-dienes as γ-dielectrophiles for A New Synthesis of Imidazole-4-carboxylates.

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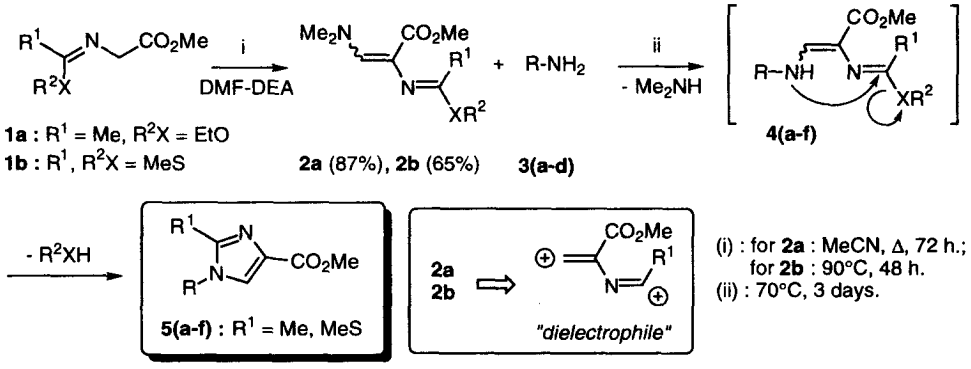
Abstract : 4-Dimethylamino 2-aza-1,3-dienes **2a,b** derived respectively from methyl N-(1-ethoxyethyliden)glycinate **1a** and methyl N-[bis-(methylthio)methylene]glycinate **1b** react with hydrazines **3a,b** and amines **3c,d** to give the corresponding new imidazole-4-carboxylates **5(a-f)** by a solvent-free aza-annulation. © 1999 Published by Elsevier Science Ltd. All rights reserved.

In view of the great utility of imidazoles derivatives as protein kinase inhibitors[1], as oral antiinflammatory agents[2], as angiotensin II receptor antagonists[3] and as fungicides[4], we found it worthwile to explore the reactivity of the 4-dimethylamino-2-aza-1,3-dienes **2a,b** as γ-dielectrophiles in aza-annulation reactions with hydrazines **3a,b** (**3a :** 1,1-dimethylhydrazine, **3b :** methoxycarbonylhydrazine) and amines **3c,d** (**3c :** phenymethylamine, **3d :** piperonylamine) (Scheme 1).

One of the continuing aims of our laboratory is to develop new synthetic routes to five membered heterocycles using solvent-free conditions[5] because of their environmentally benign and convenient work-up conditions. Herein, we wish to report the synthesis of new imidazole-4-carboxylates **5**[6] by a simple solvent-free method.

Scheme 1



The unknown starting 4-dimethylamino 2-aza-1,3-diene **2a** (R^1 = Me, R^2X = EtO) was easily prepared (87% yield) in refluxing acetonitrile during 72 hours from a mixture of imidate **1a**[7] and 1.2 equivalent of N,N-dimethylformamide diethylacetal[8] (DMF-DEA). Similarly, the dielectrophile **2b**[9] (R^1, R^2X = MeS) was synthetized by reaction of DMF-DEA with N-[bis-(methylthio)methylene]glycinate **1b**[10] using solvent-free conditions (90°C, 48 h, 85% yield).

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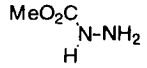
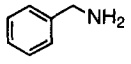
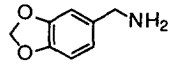
Synthesis of imidazole-4-carboxylates **5(a-f)** was readily achieved without solvent by heating a mixture of 2-aza-1,3-diene **2** with hydrazines **3a,b** or amines **3c,d** during 3 days at 70°C. This reaction was monitored by ^1H NMR spectroscopy. Analysis of the crude reaction mixture indicated the formation of the expected imidazole **5** but the transaminated[11] intermediate **4** could not be isolated. Thus, products **5** were purified by chromatography on silica gel 60F-254 (Merck). The results are summarized in Table 1. The structural assignment of the compounds **5(a-f)** is based on spectroscopic data (^1H, ^{13}C NMR, mass spectrometry). For example in ^1H NMR, **5c**[12] exhibits a low field singlet at δ 7.94 ppm assignable to H-5 and in ^{13}C NMR, two signals : one at δ 120.8 ppm for C-5 and another one at 132.4 ppm for C-4.

Table 1 : Synthesis of imidazole-4-carboxylates **5(a-f)** by solvent-free aza-annulation.

Imidazole	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**
R^1	Me	Me	MeS	MeS	MeS	MeS
Reagent **3**	**3a**	**3b**	**3a**	**3b**	**3c**	**3d**
Yield of **5** (%)[a]	65	70	60	63	62	70
mp of **5** (°C)	101-102	68-70	132-133	oil	72-74	84-86

3a :  **3b :**  **3c :**  **3d :** 

[a] Yield of isolated imidazole.

Thus, this aza-annulation reaction affords a convenient route to imidazole-4-carboxylates **5** from the 4-dimethylamino 2-aza-1,3-dienes **2** and the simplicity of the experimental procedures using solvent-free conditions renders this method particularly attractive. The extension of this strategy to other γ-dielectrophiles with functionalized amines **3** is presently in progress.

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(12) *Selected spectral data of* methyl 1-dimethylamino-2-methylthio-imidazole-4-carboxylate (**5c**) : ^1H NMR ($CDCl_3$, 300 MHz) δ : 2.65 (s, 3H); 2.80 (s, 6H); 3.88 (s, 3H); 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 13.56 (q, J = 142 Hz); 47.33 (qq, J = 136, 4.5 Hz); 51.82 (q , J = 147 Hz), 120.75 (d, J = 194 Hz, C-4); 132.39 (d, J = 6.5 Hz, C-4); 146.79 (C-2); 162.84 (CO); HRMS, *m/z* = 215.0734 found (calculated for $C_8H_{13}N_3O_2S$ requires 215.0728); mp = 132-133°C.