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# New Synthesis of 4-Amino-1-Azadienes by Addition of Zn-Enolates to Nitriles.

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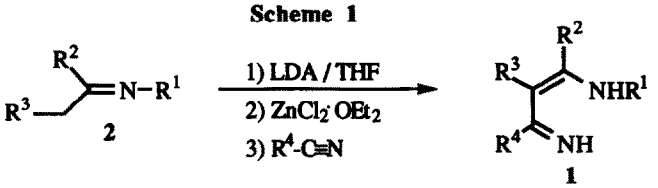
*Key words:* Synthesis; 4-amino-1-azadienes; Zn-enolates.

***Abstract:*** *A synthesis of 4-amino-1-azadienes 1 by addition of Zn-enolates of Schiff bases to nitriles is described. This method improves the yields achieved by the former one using $AlCl_3$.*

4-Amino-1-azadienes **1**, very versatile synthons in the preparation of a wide range of organic systems[1], have been usually obtained by reaction of Schiff bases **2** with nitriles, $AlCl_3$ acting as Lewis acid[2]. Nevertheless, in the course of recent investigations we found that the necessary azadienes **1** could not be prepared by the former method or were obtained in low yields. Very recently[3], we reported a new synthesis of symmetrical azadienes **1** ($R^1$=$R^3$=H, $R^2$=$R^4$) from $Cp_2TiMe_2$ (Cp=$\eta^5$-$C_5H_5$) and nitriles with excelent yields, but unfortunately, this method failed up to date in the preparation of unsymmetrical **1** ($R^2 \neq R^4$). In this sense, we describe here a new synthesis of 4-amino-1-azadienes **1** via Zn-enolates of Schiff bases.

**Scheme 1**




The Schiff base **2** was treated with LDA ($LiN^iPr_2$) in THF and the subsequent Li-enolate was converted into the Zn-enolate by addition of $ZnCl_2$ in ether. Further reaction with a nitrile led to the azadienes **1** in moderate to good yields (**Scheme1, Table 1**)[4]. This methodology substantially improves the yields obtained by the previous method using $AlCl_3$[2] (**1g-l,n Table 1**) and it allows to obtain the azadiene in suitable outcome when it is not obtained at all by the former method (**1a-f,m Table 1**). In two cases (**1e,m Table 1**) the azadiene could also be obtained by direct reaction of the Li-enolate of **2** with the nitrile, following the method depicted in **Scheme 1** omitting the addition of $ZnCl_2$. Nevertheless, other attempts made with Li-enolates (**1b,c,f,h,j,n**) and M (=Mg, B, Ti, Sn, Ce)-enolates (**1b,e**) were unsuccessful, recovering the starting materials. The absence of reactivity in the mixture **2**/nitrile/$AlCl_3$[2] would explain the results obtained with $AlCl_3$ since starting materials were detected as unique products in some cases (**1a-f,m**) and mixed with **1** in others (**1g-l,n**). This is especially relevant when a complexing group is present in the reagents far away from the C=N and C≡N bonds and competing with the nitrogen in complexing $AlCl_3$, as it occurs in $R^2$ and/or $R^4$ of **1a-f,m**. The behaviour of the M-enolates of **2** with nitriles could be supported by a higher complexing ability of nitriles towards $Zn^{2+}$, due to its higher softness in comparison with $Li^+$, $Mg^{2+}$, $BF_3$, $Ti^{4+}$, $Sn^{2+}$ or $Ce^{3+}$. In conclusion, a new and general

method for the preparation of unsymmetrical 4-amino-1-azadienes **1** by addition of Zn-enolates of Schiff bases to nitriles has been described. It must be pointed out that the azadienes **1a-f** are currently used in our laboratory to prepare potential hypolipidemic agents[5] and **1m** has been used as precursor of the N-terminal amino acid moiety of Nikkomycins B and $B_X$[6].

**Table 1. Preparation of 4-Amino-1-azadienes 1[a]**

| 1 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield(%)[b] [Zn-Enol.] | Yield(%)[b] [$AlCl_3$][c] | m.p.(°C)[d] |
|---|---|---|---|---|---|---|---|
| **a** | $^i$Pr | p-TBDMSOCH$_2$-Ph | H | Me | 54 | -[g] | oil |
| **b** | $^i$Pr | p-TBDMSOCH$_2$-Ph | H | Et | 89 | -[g] | oil |
| **c** | $^i$Pr | p-TBDMSOCH$_2$-Ph | H | $^i$Pr | 63 | -[g] | oil |
| **d** | $^i$Pr | p-TBDMSOCH$_2$-Ph | H | Ph-CH$_2$ | 68 | -[g] | oil |
| **e** | $^i$Pr | p-TBDMSOCH$_2$-Ph | H | Ph | 76 (65)[e] | -[g] | oil |
| **f** | $^i$Pr | p-TBDMSOCH$_2$-Ph | H | 2-Furyl | 81 | -[g] | 88-90 |
| **g** | p-Me-Ph | Ph | H | $^i$Pr | 65 | 37 | 130-132 |
| **h** | p-Me-Ph | Ph | H | Ph | 78 | 38 | 170-172 |
| **i** | p-Me-Ph | p-MeO-Ph | H | $^i$Pr | 77 | 27 | 100-102 |
| **j** | p-Me-Ph | p-MeO-Ph | H | Ph | 70 | 41 | 138-140 |
| **k** | p-Me-Ph | p-MeO-Ph | Me | $^i$Pr | 54 | 3 | 104-106 |
| **l** | p-Me-Ph | p-MeO-Ph | Me | Ph | 72 | 30 | 150-152 |
| **m** | p-Me-Ph | p-MeO-Ph | Me | 2-Furyl | 95 (73)[f] | -[g] | 137-139 |
| **n** | p-Me-Ph | Ph | Me | Ph | 75 | 42 | 151-153 |

[a] TBDMS=$^t$BuMe$_2$Si; all products showed satisfactory NMR data and microanalyses. [b] By $^1$H-NMR (300 MHz) of the crude mixture (estimated error ≤ ±2). [c] **2**/Nitrile/$AlCl_3$ ratio 1/10/1.5 in toluene at 100°C for 5h (ref.2). [d] Solids were recrystallized from n-hexane/chloroform. [e] Via Li-enolate. [f] Via Li-enolate using THF/(Me$_2$N)$_3$PO (30:1) as solvent. [g] **1** was not detected by $^1$H-NMR.

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4. **Typical procedure:** To a solution of LDA (2.4 mmol) in dry THF (10 ml) a solution of **2** (2 mmol) in dry THF (10ml) is added at -78°C (R$^3$=H) or at 0°C (R$^3$=Me). After 1h, $ZnCl_2$ (5ml, 1M in ether) is added and the temperature is kept for 10 min; then, the nitrile (3 mmol) is dropped. The mixture is stirred overnight to rt and heated for an additional 6h at 80°C. After cooling, 3N NaOH is poured into the mixture and the organic layer is extracted with ether, dried ($Na_2SO_4$), filtered and evaporated. Compounds **1** are purified by flash chromatography on basic alumina with n-hexane/AcOEt (5:1) (**1a-d**) or on silica gel with n-hexane/ether (5:1) (**1e-n**).
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