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SYNTHESES IN SUPERHEATED AQUEOUS MEDIA: PREPARATION OF FULLY DEUTERATED PYRAZOLES AND QUINOXALINES

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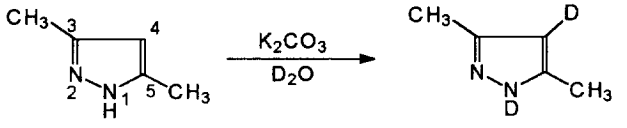
Abstract: A general, post–synthetic labeling method for the preparation of fully deuterated pyrazoles and quinoxalines by base–induced isotope exchange in superheated deuterium oxide is described. Examples include the synthesis of 2-methylquinoxaline–d_8, 2,3-dimethylquinoxaline–d_{10}, 3,5-dimethylpyrazole–d_8, and 3,5-diphenylpyrazole–d_{12}.

Key words: Deuterium labeling, basic isotope exchange, pyrazoles, quinoxalines

INTRODUCTION

Deuterated pyrazoles and quinoxalines find widespread applications, including studies of the solid state proton transfer dynamics of pyazoles,[1] the manufacture of non–linear optical materials,[2] and the preparation of standards for stable isotope dilution mass spectrometry.[3] The synthesis of these compounds from labeled precursors can be laborious and expensive,[2,4] while attempts to employ post–synthetic exchange procedures for their preparation have had limited success in the past. Thus, ethylaluminum dichloride catalyzed H–D equilibration in benzene–d_6 failed to introduce any labels as a result of complexation of the substrates.[5] Attempts to introduce deuterium labels into quinoxalines under High Temperature Dilute Acid (HTDA) conditions resulted in their rapid hydrolysis.[3] Isotopic exchange of pyrazole in positions 1 and 4 in the presence of bases has been

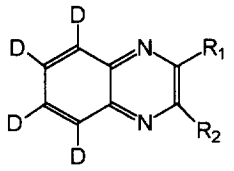
reported to occur at elevated temperatures, but it did not extend to alkyl substituents.[6] Thus, **1** was converted to **2** in the presence of potassium carbonate (Scheme 1).[4]



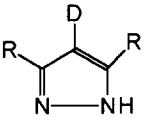
1 **2**

Scheme 1. Partial deuteration of 3,5-dimethylpyrazole under weakly basic conditions.

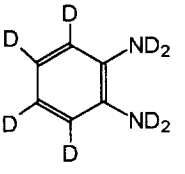
Recently, we demonstrated that base-induced isotope exchange in supercritical D_2O constitutes a general method for the preparation of deuterated arenes and heteroarenes.[7] The deuteration of aromatic substrates under subcritical basic conditions also has been reported, but examples of its application are very limited.[8,9] We have adapted these methods for the synthesis of deuterated pyrazoles **3** and **4**, and quinoxalines **5** and **6**.



3, $R_1 = R_2 = CD_3$
4, $R_1 = D$, $R_2 = CD_3$



5, $R = CD_3$
6, $R = C_6D_5$



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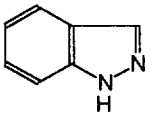

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RESULTS

Base-induced supercritical deuterium exchange (SDE) was found to be well-suited for the preparation of **5** and **6**. Titration before and after exchange indicated a *ca.* 20% loss of OH , likely resulting from side reactions (e.g., oxidation reactions with bicarbonate formation). The yield of **6** was nearly quantitative, while that of **5** was limited by the formation of unknown gaseous byproducts which will be examined in future work. While SDE also can be applied to the preparation of quinoxalines **3** and **4**, exchange is accompanied by extensive decomposition.[7] Satisfactory yields were obtained under basic subcritical exchange conditions, which limited the hydrolysis of **3** and **4** to **7**. Deuteration extended to the methyl moieties, and represents one of the few examples of $CH_3 \rightarrow CD_3$ transformation reported in the literature.[10] In contrast to the pyrazoles employed in this

study, indazole **8** was found hydrolyze completely under the conditions given below for the preparation of **3**. The chemical and isotopic compositions of the products were determined by GC–MS. Mass spectra of **2** and its protiated analog are show below as an example (Fig. 1).

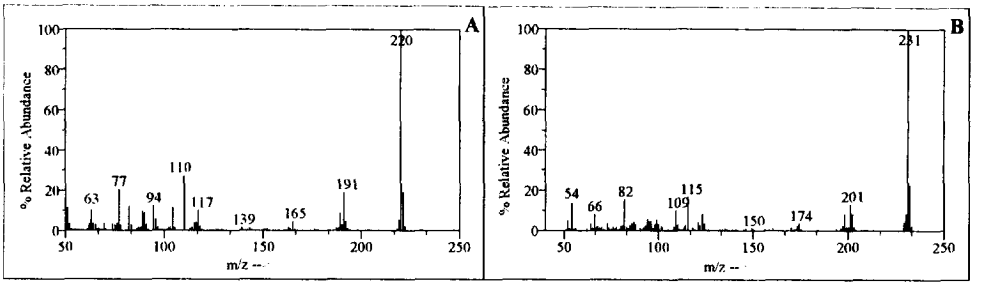

Figure 1. *Mass spectra of 3,5-diphenylpyrazole (A) and 3,5-diphenylpyrazole-d_{11}. (B).Conditions: GC inlet, EI at 70 eV.*

While there can be little doubt that compounds **5** and **6** were deuterated in position 1, no attempts were made to retain these labels during workup. Rather, isotopic purities in this position were conveniently restored by shaking with D_2O after product purification.[10]

3,5-Diphenylpyrazole-d_{11} **6** *(representative SDE procedure).* A 50 mL Hastelloy–C22 autoclave with metal–to–metal gasketing was charged with 1.50 g of 3,5-diphenylpyrazole, 20 mL D_2O, and 0.3 mL of 40% w/w sodium deuteroxide solution. The autoclave was heated to 410 ± 5 °C for 8 hrs. Pressures were inferred from PVT tables and reached approximately 500 bar. **CAUTION: High temperatures and pressures.** After cooling, the product was collected by filtration. One consecutive exchange cycle resulted in >96% isotopic purity, as evaluated by GC–MS. The yield, after flash chromatography (dichloromethane/silica gel) was 1.43 g (91%). Following the same procedure, 1.80 g 3,5-dimethylpyrazole were converted to 1.00 g (52%) 3,5-dimethylpyrazole-d_7 **5**. Exchangeable protons in position 1 subsequently were replaced by shaking with D_2O.

2,3-Dimethylquinoxaline d_{10} **4** *(representative subcritical exchange procedure).* Following an analogous procedure, exchange of 2.50 g 2,3-dimethylquinoxaline was carried out at 290 ± 5 °C for 12 hrs. The product was extracted with 2 × 10 mL dichloromethane and returned for a second

exchange step under identical conditions. The yield, after flash chromatography (dichloromethane/ silica gel) was 1.83 g (69%). Analogously, 1.62 g 2-methylquinoxaline-d_8 **3** from 2.50 g 2-methylquinoxaline (62% yield after distillation).

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