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A facile KF/Al_2O_3 mediated, selective alkylation of benzodiazepin-2,5-diones

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Abstract

We have developed a new, versatile method for the selective alkylation of benzodiazepin-2,5-diones using KF on Al_2O_3. The use of a reagent on a solid support makes this process suitable for the preparation of combinatorial libraries.

The benzodiazepines constitute an important class of biologically active compounds that have received a great deal of attention since their initial discovery in the late 1950s.[1] Members of this class have been identified as antihypertensives, angiotensin II antagonists, platelet aggregation inhibitors, gpIIb/IIIa receptor antagonists, anticonvulsives, substance P inhibitors, and antimicrobial agents.[2] A large number of these have been prepared using several published synthetic protocols. The appearance of combinatorial chemistry has increased the accessibility of benzodiazepines, as several solid phase syntheses of benzodiazepines have been published recently. In addition, solution phase preparation of libraries of benzodiazepines have also been reported.[3] Recent work in our laboratories has led to a method for the preparation of benzodiazepin-2,5-dione libraries using methodology that sits between these two options, solution phase chemistry with solid supported reagents. We have found that benzodiazepin-2,5-diones can be selectively alkylated in the presence of an alkyl bromide (or iodide) with the aid of potassium fluoride on alumina (40% KF by weight). The choice to use a solid supported reagent provides some of the advantages of both solid and solution phase chemistry. Like solid phase synthesis, excess support bound reagent can be used and removed by filtration, avoiding cumbersome aqueous work-ups. In addition, since the compound of interest is never covalently bound to the solid support, monitoring of the reactions and analysis can be accomplished using standard methods (thin layer chromatography, solution ^{1}H NMR, etc.). Finally, the products are isolated by filtration and removal of the solvents, eliminating the need for a cleavage step that is required in solid phase preparations.

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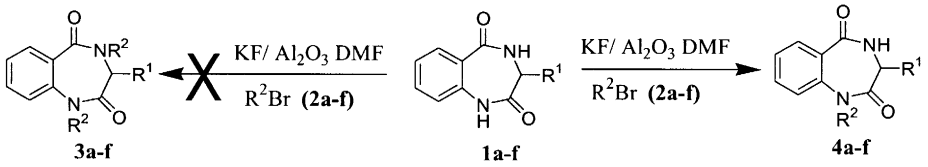
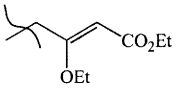
The use of potassium fluoride on alumina (KF/Al_2O_3) as a base for functionalization of amides was initially reported in 1981 by Yamawaki, but has received very little attention since then.[4] According to the literature, this method suppresses the formation of the *O*-alkylated product in favor of *N*-alkylation. We recently rediscovered this work during an examination of various potential methods for the preparation of libraries of differentially dialkylated benzodiazepin-2,5-diones. In our initial attempts to apply this chemistry to benzodiapin-2,5-diones, we expected that treatment of **1a** with 2.0 equivalents of an alkyl bromide (**2a**) in DMF in the presence of KF/Al_2O_3 would lead to the dialkylated product **3a** (Scheme 1). We were pleasantly surprised, however, to find that a single monoalkylated species (**4a**) was produced under these conditions. The dialkylated product was not observed even after 10 days under these conditions. In order to verify the site of alkylation (aniline versus benzamide nitrogen), benzodiazepine **4d** was prepared and found to be identical to that produced using Sun's method to prepare benzodiazepin-2,5-diones from isatoic anhydrides.[5] The broad applicability of this procedure has since been demonstrated by the successful alkylation of a number of benzodiazepin-2,5-diones with various alkyl bromides and side chains (Table 1).[6] Alkylation of a benzodiazepin-2,5-dione was readily accomplished with 1.0 equivalent of an alkyl bromide in the presence of KF/Al_2O_3 in DMF at 25°C over 48 h. Excess KF/Al_2O_3 was removed by simple filtration, providing the desired products in good to excellent yields and with a high degree of purity (the typical crude ^1H NMR shows little, if any, contamination with side products). The compounds in Table 1 have been prepared from a series of benzodiazepin-2,5-diones and alkyl bromides as part of a larger library of monoalkylated benzodiazepin-2,5-diones.



Scheme 1.

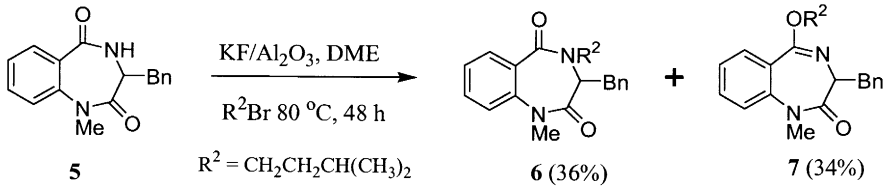
Table 1
Representative samples of monoalkylation of benzodiazepin-2,5-diones

	R_1	R_2	Yield		R_1	R_2	Yield
4a	CH_2Ph	$CH_2CH_2CH(CH_3)_2$	81%	4d*	CH_2Ph	CH_3	90%
4b	CH_3	$CH_2CH_2CH(CH_3)_2$	84%	4e	CH_2Ph	$CH_2(4\text{-}Cl\text{-}C_6H_4)$	87%
4c	$(CH_2)_2SCH_3$	$CH_2CH_2CH(CH_3)_2$	84%	4f	CH_2Ph		90%

* Iodomethane was substituted for bromomethane

In order to extend the utility of this chemistry, we attempted to find a method to alkylate the second nitrogen of a benzodiazepin-2,5-dione within a reasonable length of time. The *N*-methylated benzodiazepine **5** was used as a model. Addition of sodium iodide to transiently form the alkyl iodide did not produce any noticeable change in the rate of the alkylation of **5**. Fortunately, changing solvents had a dramatic effect on the rate of the reaction. While 1,4-dioxane showed no improvement over DMF, both acetonitrile and dimethoxyethane (DME) demonstrated significantly better results.[7] Alkylation of **5** was accomplished in 48 h when DME was used as a solvent instead of DMF, but unlike the previous chemistry, a mixture of *N*- and *O*-alkylation was observed (Scheme 2). The identity of the two different

benzodiazepines was established by examining the fragmentation patterns seen in the mass spectra of each.



Scheme 2.

Since the rates of alkylation of the two amide nitrogens of **3** are very different depending on the solvent (in DME, the dialkylated product **4** is rapidly produced), preparation of a library of differentially substituted, dialkylated benzodiazepin-2,5-diones should be possible. We are currently in the process of creating a library of this type containing several thousand compounds by scaling up the first step with a single alkyl halide and then parceling out the product to multiple reaction vessels for the second step.

In summary, we have developed a new method for the selective alkylation of benzodiazepin-2,5-diones using KF/Al_2O_3 that is suitable for the preparation of combinatorial libraries. The products are obtained in good to excellent yield and purity, allowing the preparation of both the monoalkylated and differentially dialkylated benzodiazepin-2,5-diones.

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6. Typical experimental procedure for monoalkylation of a benzodiazepin-2,5-dione: 50.0 mg (0.19 mmol) of benzodiazepin-2,5 dione **1a** and 191 mg of KF/Al_2O_3 (40% by weight) are dissolved/suspended in 3.0 ml of DMF. 28.4 mg (22.5 μl, 0.19 mmol) of isoamyl bromide is added, and the reaction is stirred at room temperature for 48 h. The reaction is then filtered and stripped to yield 51.2 mg (81%) of the desired product (**4a**). ^{1}H NMR (300 MHz, CD_3OD) 8.02 (1H, d, J=13 Hz), 7.91 (1H, t, J =8.7 Hz), 7.74 (1H, d, J=13 Hz), 7.60 (1H, t, J=8.7 Hz), 7.52 (5H, m), 4.69 (1H, dt, J=13.0, 6.5 Hz), 4.26 (1H, m, J=6.5 Hz), 3.93 (1H, m, J=5.2 Hz), 3.56 (1H, m), 3.26 (1H, dd, J=10.4, 5.6 Hz), 1.69 (1H, m), 1.56 (2H, m), 1.13 (3H, d, J=6.5 Hz), 1.04 (3H, d, J=6.5 Hz). Mass spectrum *m/z* (%): 337 (M+, 100%).
7. Typical experimental procedure for alkylation of an *N*-methyl-benzodiazepin-2,5-dione: 25 mg (0.09 mmol) of benzodiazepin 2,5-dione **5** and 75 mg of KF/Al_2O_3 (40% by weight) are dissolved/suspended in 1.2 ml of DME, and 13.5 mg (10.7 uL, 0.09 mmol) of isoamyl bromide is added. The reaction is heated to 75–80°C and stirred for 48 h. The reaction is then cooled to

room temperature, filtered, and stripped to yield 22.0 mg (70 %) of a mixture of the two desired products. Chromatography with 2/1 hexane/ethyl acetate provided 11.4 mg (36%) of the *N*-alkylated product (**6**) and 10.6 mg (34 %) of the *O*-alkylated product (**7**). ^{1}H NMR (300 MHz, CD_3OD) of **6**: 7.59 (2H, m), 7.39 (1H, d, J=11.0 Hz), 7.26 (1H, t, J=11 Hz), 7.50 (5H, m), 4.28 (1H, m), 4.17 (1H, m), 3.60 (1H, m), 3.39 (3H, s), 3.21 (2H, m), 1.80 (1H, m), 1.60 (2H, m), 0.95 (6H, m, J=8.7 Hz). Mass spectrum *m/z* (%): 351 (M+, 100%). ^{1}H NMR (300 MHz, CD_3OD) of **7**: 7.87 (0.5H, d, J=9.1 Hz), 7.78 (0.5H, d, J=11.7 Hz), 7.72, (0.5H, t, J=11.2 Hz), 7.60 (0.5H, t, J=11.2 Hz), 7.46 (1H, m), 7.41 (1H, m), 7.26 (4H, m), 7.00 (1H, m), 4.54 (0.5H, t, J=7.8 Hz), 4.43 (0.5H, dd, J=9.8 Hz), 4.05 (0.5H, m), 3.80 (0.5H, m), 3.47 (1/2H, m), 3.43 (1.5H, s), 3.39 (1.5H, s), 3.31 (1H, m), 3.00 (0.5H, m), 2.61 (0.5H, dd, J=11.1, 13.0 Hz), 2.52 (0.5H, dd, 11.0, 13.0 Hz), 1.48 (1H, m), 1.34 (2H, m), 1.00 (3H, t, J=9.8 Hz), 0.91 (3H, d, J=5.2 Hz). Mass spectrum *m/z* (%): 351 (M+, 100%).