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Regioselective Synthesis of Unsymmetrical 3,5-Dialkyl-1-arylpyrazoles

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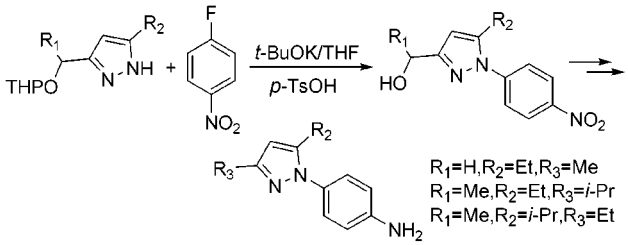
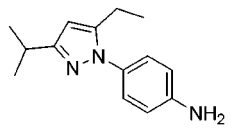
ABSTRACT



3-Alkoxylmethyl-5-alkylpyrazoles undergo regioselective N-arylation with 4-fluoronitrobenzene in the presence of base to yield the corresponding 1-(4-nitro-phenyl)pyrazoles. Further elaboration of these intermediates furnishes a practical synthesis of unsymmetrical 3,5-dialkyl-1-arypyrazoles. A tentative explanation of the observed regioselectivities is provided.

In connection with a recent medicinal chemistry program, we required a practical synthesis of unsymmetrical 3,5-dialkyl-1-arylpyrazoles. We were particularly interested in the large-scale synthesis of 3-isopropyl-5-ethylpyrazole **1** and 3-methyl-5-ethylpyrazole **2**. Aromatic substitution of N-



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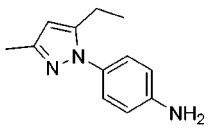

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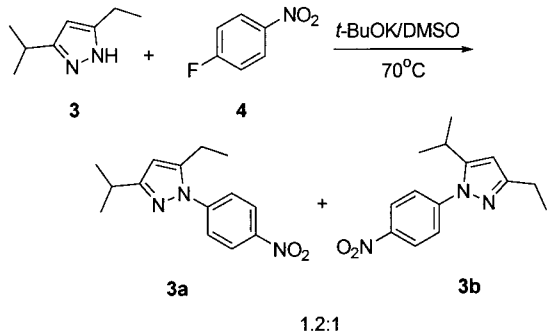
nonsubstituted pyrazoles with activated halogenated benzenes such as 4-fluoronitrobenzene has been a powerful method for synthesis of *N*-arylpyrazoles.[1] However, the reaction generally gives a mixture of two regioisomers since pyrazole is an ambident nucleophile. In an effort to directly introduce the 4-nitrophenyl on pyrazole nitrogen, we initially focused on arylation of pyrazole **3** with 4-fluoronitrobenzene **4** (Scheme 1). We anticipated that the isopropyl and ethyl groups in pyrazole **3** would have different steric requirements[2] and arylation would favor the regioisomer **3a** which would be subsequently transformed to pyrazole **1**. Surpris-

Scheme 1



(1) (a) Kost, A. N.; Grandberg, I. I. In *Progress in Pyrazole Chemistry*; Kartrizky, A. R., Boulton, A. J., Eds.; *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1966; Vol. 6, p 347. (b) Elguero, J. In *Pyrazoles and their Benzo Derivatives*; Katrizky, A. R., Rees, C. W., Eds.; *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984; Vol. 5, p 167.

(2) Wang, X.-j.; Tan, J.; Grozinger, K.; Betageri, R.; Kirrane, T.; Proudfoot, J. R. *Tetrahedron Lett.* **2000**, *41*, 5321.

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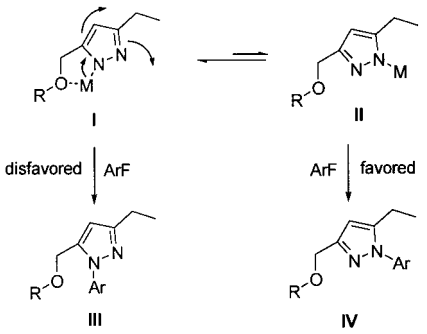
ingly, arylation of pyrazole **3** using *t*-BuOK as base in DMSO at 70 °C afforded a 1.2:1 mixture of pyrazoles **3a** and **3b**.[3] Although a careful chromatographic purification separated the two isomers, it was clearly an impractical approach to the pyrazole **1**, which we needed in a large quantity. By extension, one can suppose that this approach would not furnish a practical synthesis of pyrazole **2**.

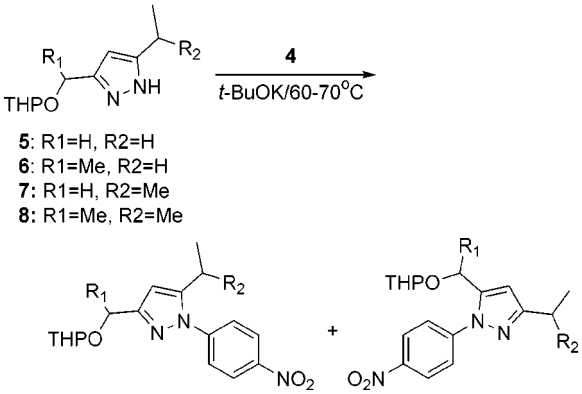
As shown in Scheme 2, we envisioned that the presence of an appropriately positioned chelating group such as **I**

Scheme 2



might block access of the electrophile and favor arylation on the pyrazole anion **II**, leading regioselectively to *N*-arylpyrazole **IV**.[4] The alkoxy group of **IV** could be further converted to the isopropyl group in **1** and methyl group in **2** later in the synthesis. We began this study with pyrazole **5**, and the related results are summarized in Scheme 3.

Scheme 3

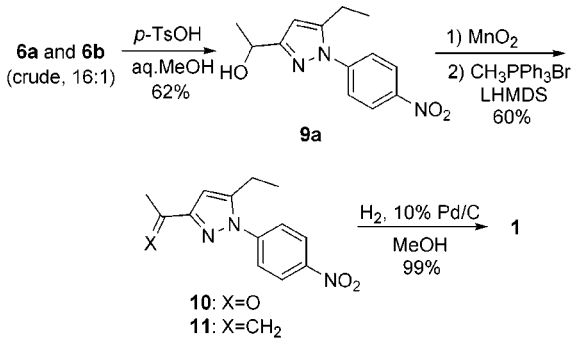


5a/5b: 7:1(THF, 71%); 1:1(DMSO, 93%)
6a/6b: 16:1(THF, 73%); 2:1(DMSO, 90%)
7a/7b: 4:1(THF, 74%); 1:1(DMSO, 94%)
8a/8b: 11:1(THF, 80%); 1:1(DMSO, 91%)

Arylation was first carried out with 4-fluoronitrobenzene using *t*-BuOK as base in DMSO at 70 °C for 1 h, and a 1:1 mixture of regioisomers **5a** and **5b** was obtained. When THF was used as solvent instead of DMSO, arylation produced a 7:1 mixture of **5a** and **5b**, in agreement with a chelation effect. The same reaction was conducted in THF using *t*-BuOLi, NaH, and EtMgBr as bases, respectively, and a very similar ratio of **5a** and **5b** was obtained in each case. These bases showed sluggish reactions with less conversion compared with the potassium salt. Arylation of pyrazole **6** in THF yielded products **6a** and **6b** in a ratio of 16:1, suggesting that a stronger chelation effect by the branched ether side chain led to a significant improvement of regioselectivity, in agreement with the Thorpe−Ingold effect. Here as well, DMSO as solvent gave a 2:1 mixture of isomers **6a** and **6b**. With pyrazoles **7** and **8**, both bearing a larger R_2 group (*i*-Pr), arylation yielded regioisomers **7a** and **7b** as a 4:1 mixture and **8a** and **8b** as a 11:1 mixture in THF, respectively, in contrast to 1:1 mixtures in DMSO. The regioselectivity for the latest two cases is slightly lower than those of **5** and **6**, probably due to the presence of the more steric demanding *i*-Pr group.

Using the newly devised approach to control regioselectivity, a practical synthesis of pyrazole **1** was achieved as outlined in Scheme 4. The THP groups of the mixture of **6a**

Scheme 4



and **6b** were deprotected with *p*-TsOH in aqueous methanol, and major isomer **9a** was isolated in 62% yield over three steps[5] simply by crystallization of the crude material in a 4:1 mixture of hexane and ethyl acetate. MnO_2 oxidation of **9a** followed by the Wittig reaction of the resulting ketone **10** gave vinyl compound **11** in 60% yield. Reduction of the double bond and nitro group in **11** was conducted in one pot with 10% Pd/C under H_2, yielding pyrazole **1**.

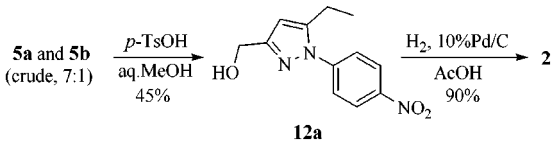
As for the scale-up of pyrazole **2**, the crude mixture of **5a** and **5b** (7:1) was similarly treated with *p*-TsOH in aqueous methanol. The resulting major isomer **12a**, free of its regioisomer **12b**, was isolated in 45% yield over three steps[5] by recrystallization from 4:1 mixture of hexane and ethyl acetate (Scheme 5). On treatment of **12a** with 10% Pd/C under H_2 in the presence of concentrated HCl, pyrazole **2**

(3) Malhotra, N.; Falt-Hansen, B.; Becher, J. *J. Heterocycl. Chem.* **1991**, *28*, 1837.

(4) (a) Brunner, H.; Scheck, T. *Chem. Ber.* **1992**, *125*, 701. (b) Luo, Y.; Potvin, P. G. *J. Org. Chem.* **1994**, *59*, 1761. (c) Tarrago, G.; Ramdani, A. *J. Heterocycl. Chem.* **1980**, *17*, 137. (d) Khan, M. A.; Lynch, B. M. *J. Heterocycl. Chem.* **1970**, *7*, 1237.

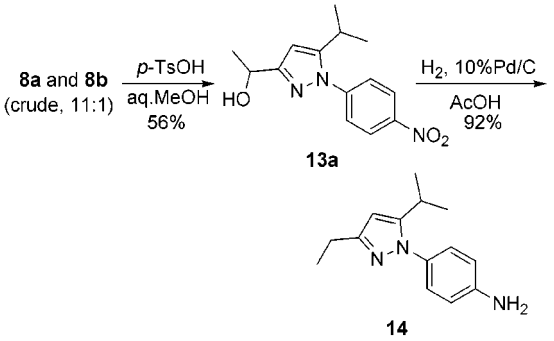
(5) Pyrazoles **5**−**8** were made from condensation of their corresponding propargylic ketones with hydrazine and used directly without purification.

Scheme 5



was obtained in excellent yield. 3-Ethyl-5-isopropylpyrazole **14**, the regioisomer of **1**, was made from deprotection of the crude mixture **8a**/**8b**, followed by hydrogenation of the isolated major alcohol **13a** (Scheme 6).[6] This newly devised

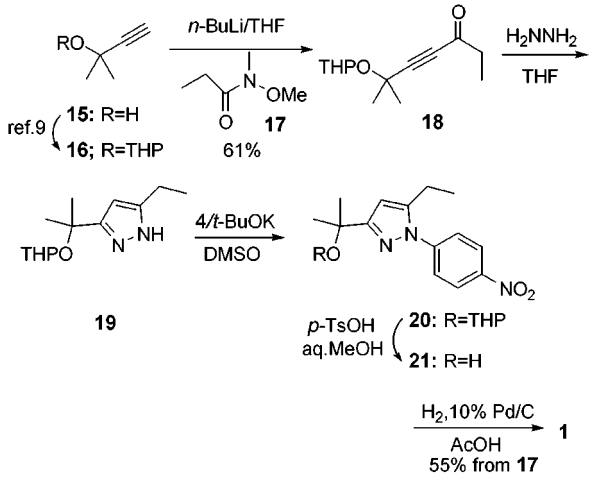
Scheme 6



approach can certainly be extended to synthesis of unsymmetrical *N*-arylpyrazoles bearing alkyl groups at the 3 and 5 positions, considering the good recovery of the intermediates **9a** (62% yield), **12a** (45% yield), and **13a** (56%) without chromatography. These intermediates could be easily converted into a variety of analogous pyrazoles by functionalization of the hydroxy groups.

Encouraged by the regioselective arylation of **6**, we anticipated a substrate such as **19** with one more methyl substituents on its side chain should have a stronger chelation compared with that of **6**. N-Arylation under the same condition would therefore highly favor the regioisomer **20**, which is readily converted to **1**. It may also be true that the tertiary carbon of pyrazole **19** is sterically hindered enough to effect a high degree of regioselectivity for N^1-arylation.[3,7,8] Thus, starting from commercially available 2-methyl-3-butyn-2-ol (**15**), THP ether **16** was prepared in 93% yield[9] and was treated with *n*-BuLi at −30 °C followed by amide **17** leading to the propargylic ketone **18** in 61% yield after

Scheme 7



high vacuum distillation (Scheme 7). Condensation of **18** with hydrazine in THF at room temperature yielded pyrazole **19**, which was directly subjected to aromatic substitution without purification. Displacement of 4-fluoronitrobenzene with pyrazole **19** in DMSO gave **20** as a single product as anticipated. Subsequent treatment of the resulting crude **20** with a catalytic amount of *p*-TsOH in aqueous methanol led to pyrazole **21** quantitatively. Pyrazole **21** was then subjected to hydrogenation with 10% Pd/C in acetic acid under 40 psi of H_2 for 24 h yielding pyrazole **1**, which was purified by recrystallization from a mixture of hexane and ethyl acetate with a recovery of 55% from **18**. This facile process involved no chromatography and the intermediates **18** through **21** needed no purification.

In conclusion, we have developed a new regioselective approach toward unsymmetrical 3,5-dialkyl-1-arylpyrazoles. On the basis of the observed results in solvents of different polarity (DMSO and THF), it seems likely that association between the substrate and the cation may play the major role in directing the reaction.[10] Given the different outcomes in the two solvents, substituent sterics alone cannot be responsible for the observed selectivities and the model in Scheme 2 appears to explain all our currently available data. As a result, an efficient synthesis of 3-isopropyl-5-ethylpyrazole **1** and 3-methyl-5-ethylpyrazole **2** was achieved.

Acknowledgment. We wish to thank Dr. John R. Proudfoot for helpful discussions during the course of this work.

Note added after ASAP: Due to a processing error, this Letter was posted ASAP on 9/2/00 with incorrect graphics for Schemes 1 and 2. The correct version was posted on 9/7/00.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, **2**, **3a**, **3b**, **5**, **9a**, **9b**, **10**, **11**, **12a**, **12b**, **13a**, **13b**, **14**, and **17**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The structures of all regioisomers were supported by NOE experiments.

(7) Elguero, J.; Gonzalez, E.; Jacquier, R. *Bull. Soc. Chim. Fr*. **1968**, 707.

(8) 3-*tert*-Butyl-5-ethylpyrzole (**22**) was subjected to the same N-arylation with 4-fluoronitrobenzene to give 1-(4-nitrophenyl)-3-*tert*-butyl-5-ethylpyrzole (**23**) as a single regioisomer.

(9) Chavez, F.; Godinez, R. *Synth. Commmun*. **1992**, *22*, 159.

(10) To support our rationale, N-arylation of **5** was carried out using KO*t*-Bu as base in the presence of 1 equiv of 18-crown-6 in refluxing THF. The reaction gave a 1:1 mixture of regioisomers **5a** and **5b**, in contrast with a 7:1 mixture obtained without 18-crown-6.