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Regioselective Synthesis of 1,3,5-Triaryl-4-alkylpyrazoles: Novel Ligands for the Estrogen Receptor

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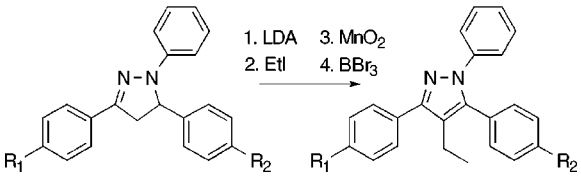
ABSTRACT



A regioselective synthesis of 4-alkyl-1,3,5-triarylpyrazoles has been developed for the preparation of unsymmetrically substituted systems of interest as ligands for the estrogen receptor.

In our efforts to discover novel ligands for the estrogen receptor (ER) that might act as selective estrogen receptor modifiers (SERMs),[1] we found that 1,3,5-triaryl-4-alkylpyrazoles such as **1** and **2** (Scheme 1) were good ligands for ER, demonstrating high binding affinities and transcriptional efficacy that in some cases were very selective for the ER α subtype (ERα).[2,3] Initially, we synthesized these pyrazoles by condensation of 2-alkyl-1,3-diketones with arylhydrazines.[4−6] Of course, when the 1,3-diketones were unsymmetrical, this approach did not afford any significant regioselectivity. This lack of regioselectivity became of concern when we needed the corresponding monophenols **3** and **4** for structure−activity studies to determine which phenol in pyrazole **2** mimics the A-ring of estradiol. According to a classical approach, the monophenol with the higher affinity can be presumed to be the one that corresponds to the A-ring of estradiol.[7,8] However, when the original 1,3-dione−hydrazine condensation pyrazole synthesis was used to prepare these monophenols, only an inseparable mixture of the two regioisomers **3** and **4** was afforded (Scheme 1). Thus, a regioselective approach to these and related compounds was needed.

In a related effort, we wanted to develop these novel 1,3,5-triaryl-4-alkylpyrazole ligands into the sort of mixed agonist/antagonists that typically have SERM activity.[9,10] This generally involves incorporating a basic or polar side chain (such as a piperidinylethoxy group) onto either the C(3) or C(5) phenyl groups. However, when pyrazoles **6** and **7** were prepared by condensation of 4-methoxyphenylhydrazine with unsymmetrical 1,3-diketone **5**, we obtained the regiosiomeric pyrazoles **6** and **7** in pure form only after exhaustive chromatography, and we had to obtain an X-ray structure of the more crystalline isomer **6** to establish the identity of these regioisomers (Scheme 1).

The results from cell-based transcriptional assays showed that pyrazole **7** has the desired antagonistic character typical for a SERM. However, to examine this series further we

(1) Grese, T. A.; Dodge, J. A. *Curr. Pharm. Des.* **1998**, *4*, 71−92.
(2) Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. *Chem. Biol.* **1999**, *6*, 205−219.
(3) Stauffer, S. R.; Katzenellenbogen *J Comb. Chem.* **2000**, *2*, 318−329.
(4) Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. *Chem. Biol.* **1999**, *6*, 205−219.
(5) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Submitted.
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(9) Grese, T. A.; Dodge, J. A. *Curr. Pharm. Des.* **1998**, *4*, 71−92.
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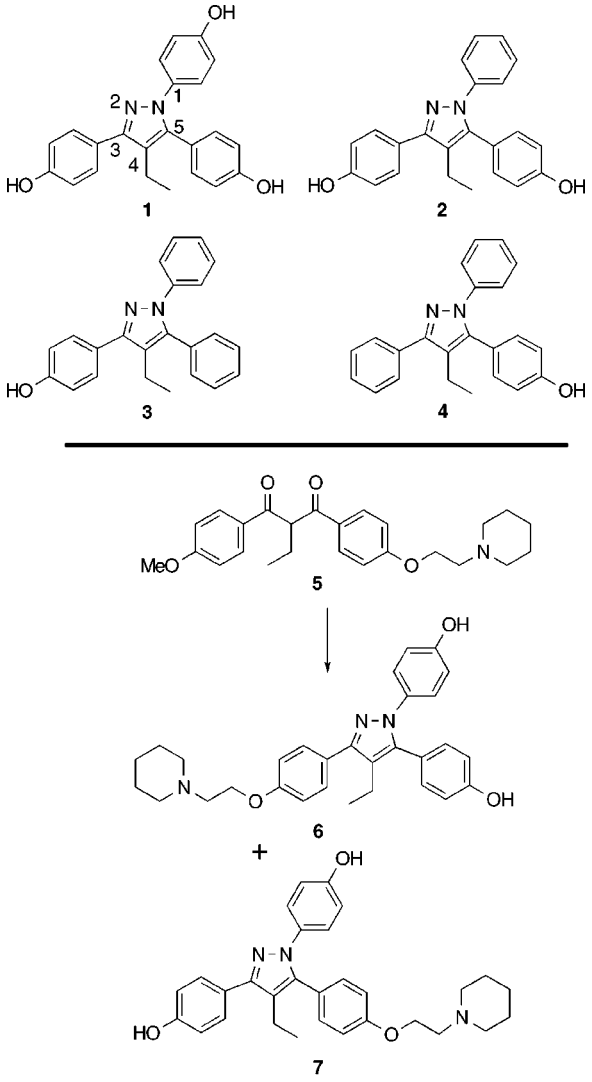
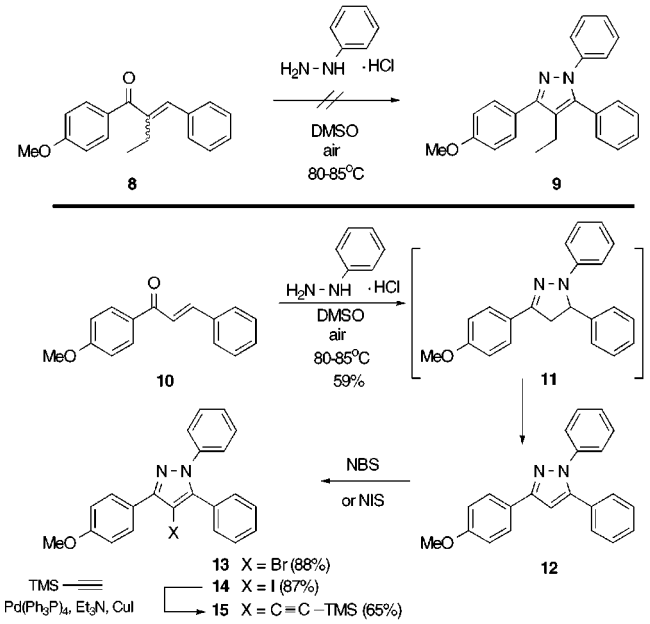
Scheme 1. Pyrazole Ligands for the Estrogen Receptor α



Scheme 2. Regiospecific Preparation of 1,3,5-Triaryl-4-halopyrazoles and Their Reactions



required a regioselective method for the synthesis of the basic side chain derivatives of these 1,3,5-triaryl-4-alkylpyrazole systems.

Regioselective Synthesis of the Monophenolic Tetrasubstituted Pyrazoles (3 and 4). To develop a regioselective synthesis of these tetrasubstituted pyrazoles, we investigated the reaction of α,*β*-unsaturated ketones with arylhydrazines, having as our initial goal the synthesis of the two monophenolic pyrazoles **3** and **4** (Scheme 2). Although α,*β*-unsaturated ketone **10** condensed smoothly with phenylhydrazine to afford a single pyrazole product, **12**, its α-substituted counterpart **8** failed to react under these conditions. The regioisomeric structure of **12** was assigned on the basis of a similar type of reaction reported in the literature,[11,12] although the mechanism that accounts for the regioselectivity was not clear at this point (vide infra). Pyrazole **12** was presumed to be formed through oxidation of the initially formed dihydropyrazole (pyrazoline **11**), although it was not certain whether air (the reaction was run in air) or dimethyl sulfoxide served as the oxidant for this transformation. On the basis of these observations, we investigated methods to introduce the 4-alkyl substituent after the formation of the pyrazole system **12**.

When deprotonation at the 4-position of **12** with *s*-BuLi followed by trapping with ethyl iodide failed to give the desired product, we turned our attention to routes through the corresponding bromide **13** and iodide **14**, which were readily prepared from pyrazole **12** by treatment with the corresponding halo succinimide in CH_2Cl_2 at room temperature. When bromide **13** was treated with *n*-BuLi followed by ethyl iodide, pyrazole **12** was the only isolated product. In our attempts to effect ethyl or vinyl group substitution at C(4) of iodide **14** using various transition metal-mediated reactions (Pd, Ni), we isolated only the reduction product **12** and starting iodide **14**, suggesting that *β*-hydride transfer competes with reductive elimination in this hindered system. Consistent with this is the fact that we were only able to introduce an acetylene group (producing **15**) or aryl group (not shown) by this approach.[13]

Because of the difficulties we encountered in introducing the C(4)-alkyl substituent in these heterocycles *after* the pyrazoles had been formed, we wondered whether we might be able to intercept the pyrazoline intermediate and introduce the alkyl substituent *before* its oxidation to the pyrazole. Indeed, by carrying out the enone−arylhydrazine condensation reaction under an inert atmosphere and eventually using

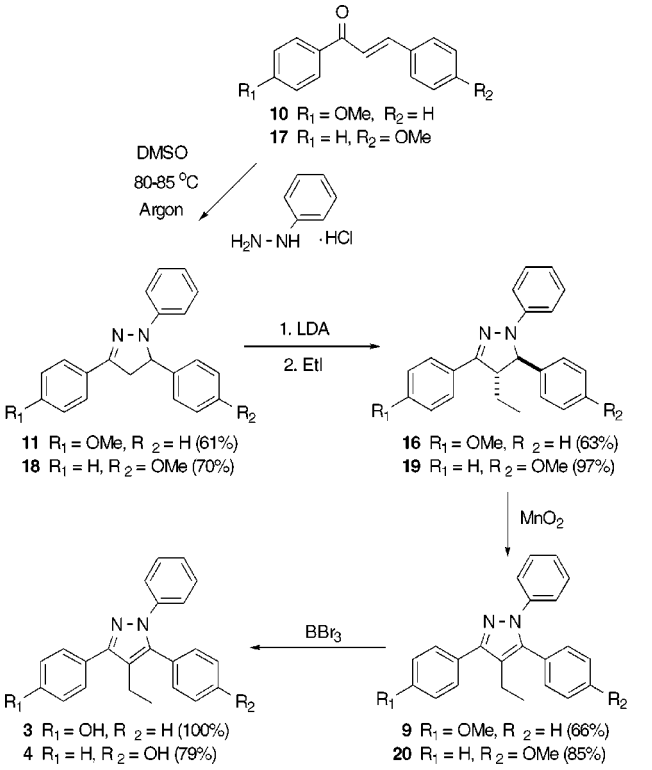
(11) Elguero, J. In *Comprehensive Heterocyclic Chemistry*, Vol. 5; Katrizky, Rees, Eds.; Pergamon: Oxford, 1985; Vol. 5, p 167.

(12) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, Rees, Scriven, Eds.; Pergamon: Oxford, 1996; p 1.

(13) Routes involving palladium-mediated coupling of aryl groups to other pyrazole systems have been described: ref 5 and Wang, X.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* **2000**, *41*, 4713−4716.

DMF as solvent in place of DMSO, we were able to isolate the air-sensitive pyrazoline intermediate **11** in 61% yield (Scheme 3). Deprotonation of the acidic C(4) methylene

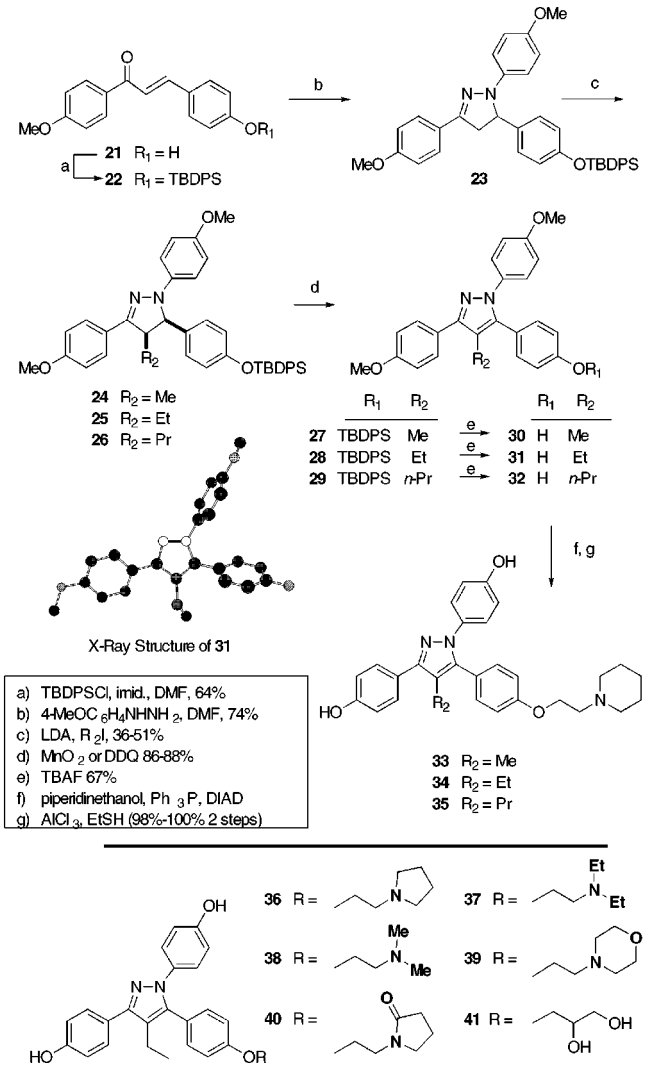
Scheme 3. Regioselective Synthesis of 1,3,5-Triaryl-4-alkylpyrazoles **3** and **4**



group of **11** with LDA at −78 °C in THF, followed by trapping of the resulting anion with ethyl iodide, afforded ethyl-substituted pyrazoline **16** (as a racemate) in 63% yield, with only small amounts of pyrazole **12** as the side product. Pyrazoline **16** was formed as a single diasteomer, and the 4,5-substituents are presumed to be trans to each other, based on the 3.7 Hz vicinal coupling constant between the two methine protons.[14] In contrast to the air-sensitivity of its unsubstituted counterpart **11**, the C(4)-alkylated pyrazoline **16** is reasonably stable. It can be stored for a prolonged period of time without apparent oxidation or decomposition, and subsequent oxidation to the corresponding pyrazole actually requires rather harsh conditions. Initially, we used MnO_2, either at high temperature (reflux benzene) or with ultrasonic agitation, and we obtained the desired 1,3,5-triaryl-4-alkylpyrazoles **9** in 66% yield, but the reaction took 48 h.

(14) Vicinal coupling constants were calculated using the Karplus relationship within Macromodel v7.0. Monte Carlo conformational searches were conducted using the Amber force field with CHC13 as a solvent model. All generated conformers from Monte Carlo searches underwent full matrix assisted minimization using the FMR function with a convergence criteria of 0.001 kcal/mol, and the Boltzman-averaged constants for the cis and trans compounds are estimated to be 9.3 and 4.8 Hz, respectively. Thus, pyrazolines **16** and **19** are presumed to be the trans isomers. NOE experiments on these pyrazolines gave ambiguous results regarding stereochemistry. See also: Hassner, A.; Michelson, M. J. *J. Org. Chem.* **1962**, *27*, 3974. Elguero, J.; Marzin, C. *Bull. Soc. Chim. Fr.* **1970**, 3466.

Scheme 4. Regioselective Synthesis of Pyrazole **7** and Its Derivatives (**36**−**41**)



Later, DDQ was found to be a more efficient oxidant. After demethylation of the protected pyrazole **9** with BBr_3, we obtained the first desired monophenolic pyrazole **3**. The other desired monophenolic pyrazole (**4**) was obtained by the same reaction sequence, starting from enone **17**. Although it is apparent that the two regioisomers **3** and **4** are different and we were quite confident in our structural assignments based on literature precedent,[15−18] the regioselectivity of this route was firmly established only later, by X-ray crystallography (vide infra).

With both pyrazole isomers **3** and **4** in hand, we determined their relative binding affinities for ER and, as described elsewhere,[5] we were able to conclude that the C(3) phenol of these pyrazoles is the ring that mimics the A-ring of estradiol.

Regioselective Synthesis of Tetrasubstituted Pyrazoles with Basic Side Chains (7, 33−41). For the synthesis of

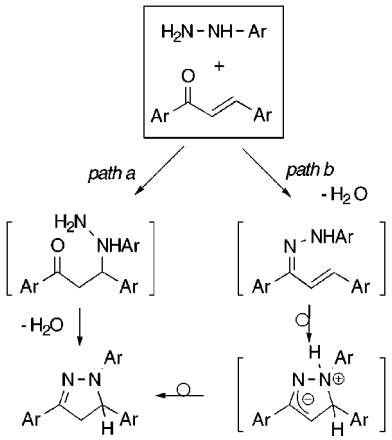
(15) Sangwan, N.; Rastogi, S. N. *Indian J. Chem.* **1979**, *18B*, 65.
(16) Gupta, S.; Rastogi, S. N. *Indian J. Chem.*. **1995**, *34B*, 245.
(17) Kaufman, F. B.; Engler, E. M. *J. Am. Chem. Soc.* **1979**, *101*, 547.
(18) Marzinzik, A. L.; Felder, E. R. *J. Org. Chem.* **1998**, *63*, 723.

pyrazole **7** and its analogues, we prepared α,β−unsaturated ketone **21** by an aldol condensation of 4-methoxyacetophenone and *p*-hydroxybenzaldehyde, according to a literature procedure[19] with modifications (Scheme 4). Despite numerous attempts, we were unable to obtain good yields in this simple reaction. However, we were able to isolate the highly crystalline enone **21** easily.

Enone **21**, protected as its silyl ether (**22**), reacted with 4-methoxylphenylhydrazine to give pyrazoline **23**. This material was alkylated, as before, with various iodides to give pyrazolines **24**−**26**, which were oxidized with either MnO_2 or DDQ to afford the desired pyrazoles **27**−**29**. Fluoride ion cleavage of the silyl group the gave the C(5) phenolic pyrazoles **30**−**32**. An X-ray structure of one of these pyrazoles (**31**, Scheme 4) secured the structure of this compound, in the process confirming the regioselectivity of this route to pyrazoles. Installation of the piperidinylethoxy side chain was accomplished by a Mitsunobu reaction. Although BBr_3 cleaved all three ether groups, $AlCl_3$−EtSH selectively cleaved only the methyl ethers, leaving the basic side chain unaffected and giving pyrazoles **33**−**35** in very high yield. A number of other side chain derivatives (**36**−**41**) were prepared in the C(4) ethyl series. Pyrazole **41** was prepared by a closely related route (not shown). We are currently investigating the biological activities of all of the new pyrazole compounds bearing the various polar/basic side chains.

Basis of Regioselectivity. The regioselectivity of this pyrazole synthesis derives from the initial enone−arylhydrazine condensation, which results in the attachment of the aryl-substituted hydrazine nitrogen to the enone β-carbon and the unsubstituted hydrazine nitrogen to the enone carbonyl carbon. Two mechanisms seem plausible for this transformation (Scheme 5), and they differ in the timing of bond formation. In path a, the aryl-substituted nitrogen reacts first, undergoing a Michael-type addition to the β-carbon of the enone which is followed by an intramolecular imine formation between the carbonyl group and the free amine. In path b, imine formation between the unsubstituted nitrogen and the carbonyl group occurs first, this being followed by a cyclization process to a zwitterionic species that undergoes proton tautomerization to furnish the pyrazoline. Whereas pathway b might first appear to be an ionic 5-endo-trig process, it can more reasonably be considered to be a concerted, symmetry-allowed closure of a 1,2-diaza analogue

Scheme 5. Possible Mechanistic Pathways for the Regiospecific Formation of Pyrazolines



of a pentadienyl anion to a 1-azaallyl anion. No intermediates are observed in this transformation. Thus, at this point, there is no definitive basis for favoring one mechanism over the other. However, the fact that α-substituted unsaturated ketones (e.g., **8**) fail to react under conditions where the unsubstituted congeners (e.g., **10**) react well (see Scheme 2) would be more consistent with mechanism a.

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Supporting Information Available: Procedures for the preparation of all of the compounds mentioned in this paper and their spectroscopic characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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