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TWO-STAGE SONOGASHIRA COUPLING METHOD IN THE SYNTHESIS OF AUXIN ACTIVE ACETYLENES

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Abstract - A sequential Sonogashira coupling of a protected acetylene precursor with aryl halides (**5**) followed by pyrazolyl iodides (**14**) allows efficient access to the unsymmetrical aryl-heteroarylacetylene (**8**). Subsequent regioselective lithiation exchange followed by dimethyl oxalate quench produced readily vicinal ketoesters (**9**) which show auxin effects in a wide variety of plant species.

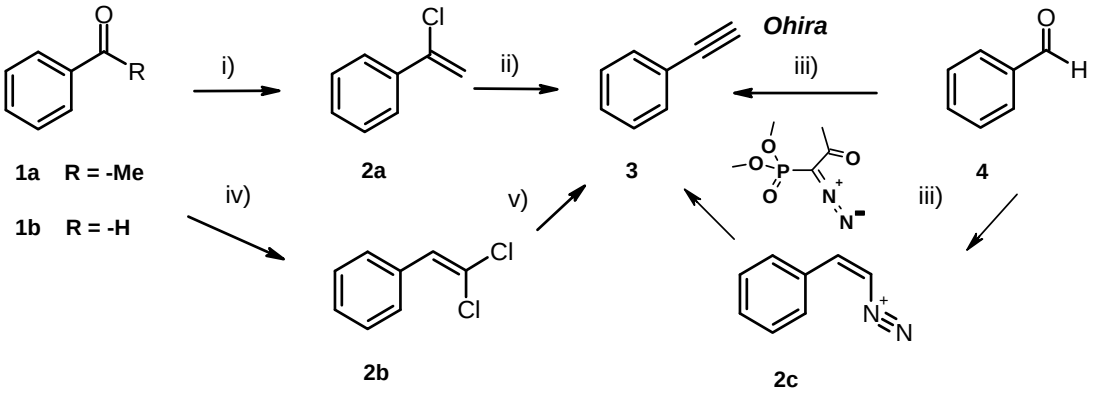
Dedicated to Professor Kevin M. Smith, vice-chancellor of Louisiana State University and recipient of the *Robert Burns Woodward Award on Lifetime Achievement* at the International Conference on Porphyrins and Pthalocyanines (ICPP- 4) held in Rome 2006.

INTRODUCTION

Throughout the agrochemical industry, synthetic chemistry has sought to solve the growing needs for better and more efficient crop protection from harmful insects, fungi or pernicious plants. Strategies for chemistry innovation are addressed through introduction of novel heterocycles,[1a,1b] application of new technologies,[2a] or simple replacement of key atoms with biosteric equivalents.[2b] In this publication we describe one such application of the ever growing usage of palladium coupling methodology in agrochemistry.[3]

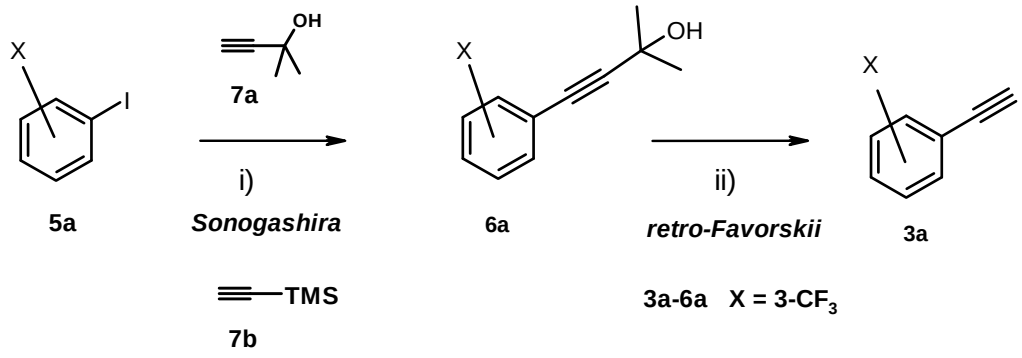
Palladium catalyzed coupling of terminal acetylenes via the Sonogashira reaction[4a] has become a mainstay procedure in organic synthesis.[4b] The application to heterocycles, particularly pyrazoles have shown unexpected problems due to vicinal functionality[5a] or deiodination[5b] but otherwise appear suitable

for synthetic elaboration.[6] Herein we describe a methodology to prepare stepwise unsymmetrical bis-aryl-pyrazolylacetylenes followed by introduction of a desired vicinal ketoester. Although alternative strategies exist for introduction of the acetylene unit into a molecule, they often rely on transformation of preexisting functionality. An example is the Corey-Fuchs method[7a] which transforms acetophenones (**1a**) from 2-chlorostyrenes (**2a**) with eventual elimination under strong basic conditions to the desired acetylene (**3**). On the other hand the Ohira reagent,[7b] achieves this in a combined retro-Claisen-Wittig reaction of benzaldehyde (**4**) presumably followed by mild β-elimination of



Reagents and Conditions: i) PCl_5, KOH. ii) n-butyllithium, THF. iii) MeOH, K_2CO_3. iv) Cl_3CCO_2Na, DMF, rt. v) Zn metal, AcOH

Scheme 1



Reagents and Conditions: i) $PdCl_2(Ph_3P)_2$, Cu (I) iodide, diisopropylamine, Ph_3P, 60 ˚C, **7a**. ii) NaOH powder and distillation. **3a** (X = 3-CF_3), 62 % from **5a**.

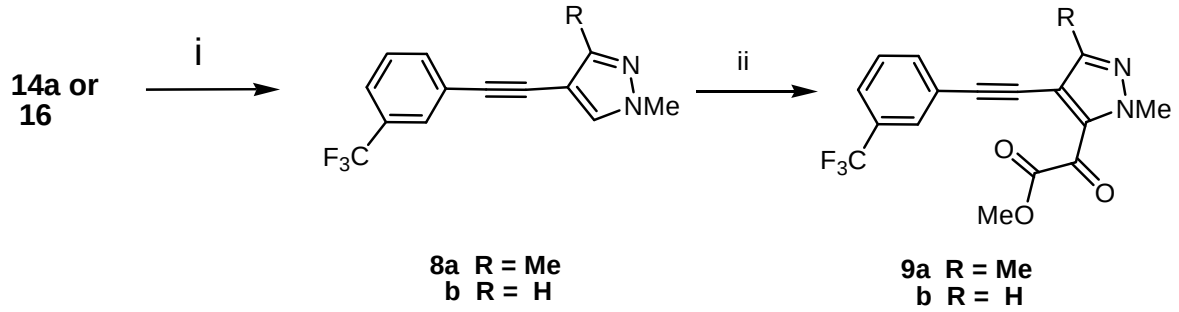
Scheme 2

diazonium ion to give the terminal acetylene.[7c] A non-Wittig variation is the formation of the vinyl dichloride (**2b**) from benzaldehyde (**1b**) and mild treatment with sodium trichloroacetate followed by

halogen elimination of the vinyl dichloride (**2b**) with zinc metal and acetic acid to the desired phenylacetylene (**3**) (Scheme1).[7d] Our strategy is exemplified by first halobenzene coupling with the acetylene precursor (**7a**), followed by a second halopyrazole coupling both using Sonogashira conditions (Scheme 2).

RESULTS AND DISCUSSION

We employed the method of Rossi *et al*. which was reproducible at large-scale conditions.[8] In general, readily available 1,1-dimethyl-2-propyn-1-ol (**7a)** was efficiently coupled with a variety of substituted halobenzenes (**5**) in 69-90 % yields. The subsequent arylpropargylic alcohols (**6**) were then distilled with added solid sodium hydroxide to give retro-Favorskii cleavage of acetone at an efficient rate to inhibit polymerization. Next a second Sonogashira coupling with iodopyrazoles (**14a, b**, **16**) allowed synthetic entry to the desired unsymmetrical acetylene (**8**). A variety of substituted phenylacetylenes coupled in typical yields of 65-85 % (Scheme 3). In contrast to alkylation conditions used in the literature[9a,9b] for preparing the starting *N*-1-methyl-4-iodopyrazoles (**14**) and (**16**), we prepared them on



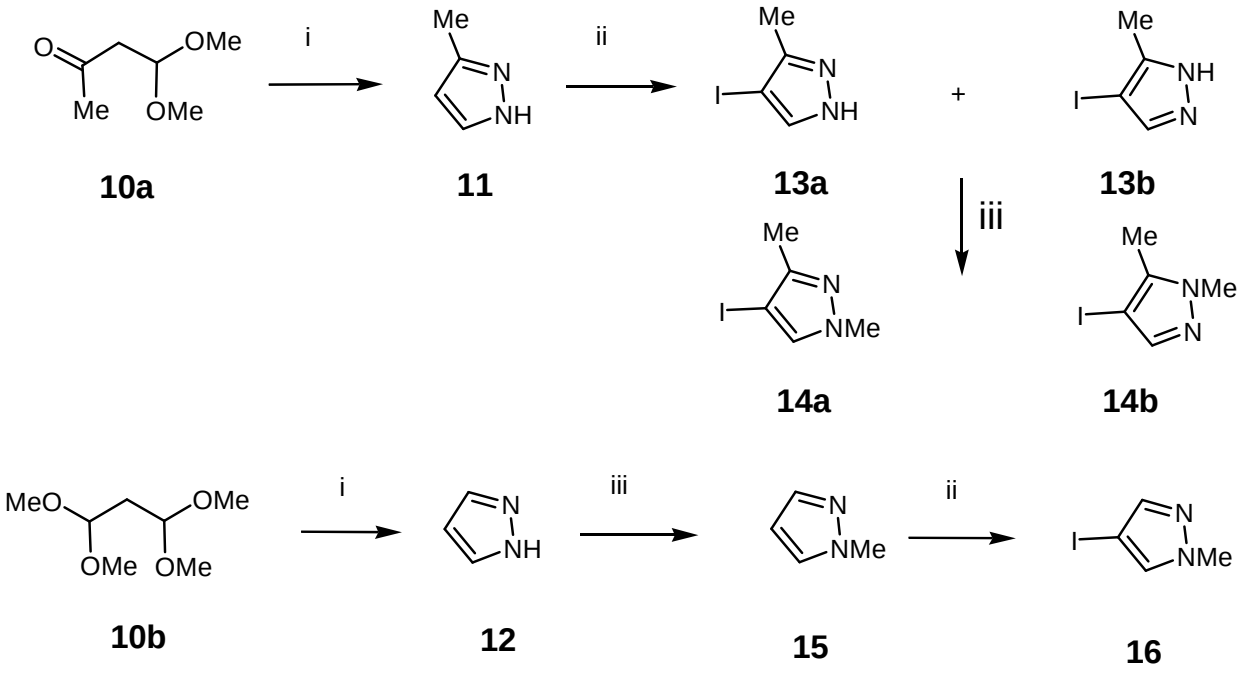
8a R = Me
b R = H

9a R = Me
b R = H

Reagents and Conditions: i) $PdCl_2(Ph_3P)_2$, Cu (I) iodide, Ph_3P, diisopropylamine, 60 ˚C, **3a**, (**8a:** 89 %, **8b:** 67 %). ii) n-butyllithium, THF, -70 ˚C, dimethyl oxalate, -60 ˚C, (**9a:** 95.6 %, **9b:** 90 %).

Scheme 3

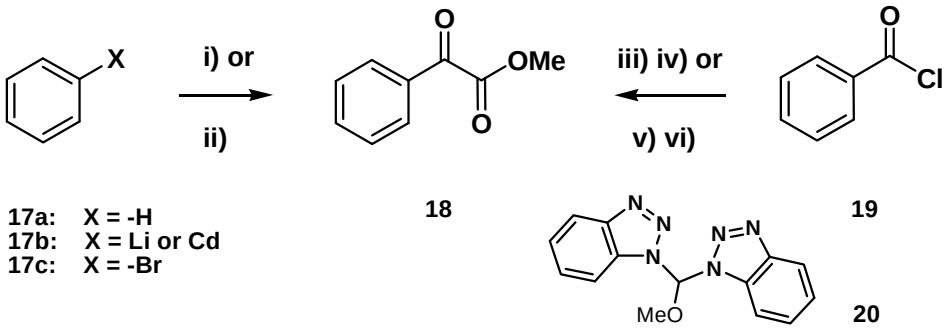
large scale in three steps utilizing phase-transfer conditions (Scheme 4). Although both iodination and alkylation steps resulted in mixtures of regioisomers (**13a,b**) and (**14a,b**) as observed by GC analysis, the products are easily separated by solubility differences in *n*-hexane following the two-step process. This permitted efficient purification of the desired pyrazole product in multigram quantities (**14a**) in 32 % overall yield. Ideally, a one-pot-two-step-coupling methodology would be an optimal improvement but this may require an amenable acetylene precursor where convenient *in situ* generation can be done.



Reagents and Conditions: i) 24 % soln. hydrazine hydrate, AcOH, 30-85 ˚C (**11**; 60 %, **12**, 90 %). ii) HIO_3, I_2, CCl_4, H_2O-AcOH, 60 ˚C (**14a**, 26 %, **14b**; 24 %; **16**, 97 %). iii) *n*-Bu_4NHSO_4, Me_2SO_4, NaOH (aq), CH_2Cl_2, (**13a: b**, 81%, **15:** 53 %).

Scheme 4

Although trimethylsilylacetylene (**7b**) is a convenient acetylene precursor it is extremely expensive. On the other hand Vasilevsky and Elguero[10] have explored the direct usage of acetylene itself. They addressed the volatility problem by application of higher boiling DMF and increased reactivity with the use of stronger bases, however their conditions gave only modest 24-35 % yields when coupled to pyrazoles in a one-pot-two-step-coupling strategy. Therefore we preferred to focus on a sequential-two-stage-coupling process.



Reagents and Conditions: i) $AlCl_3$-$ClCOCO_2Me$ (**17a**). ii) $ClCOCO_2Me$ (**17b**). iii) trimethylsilyl cyanide. iv) H_2SO_4-MeOH. v) LDA, THF, (**17c**), (**20**). vi) Amber lite-H^+ resin, MeOH.

Scheme 5

In the literature, vicinal ketoesters have been introduced by Friedel-Crafts acylation,[11a] homologation of acylcyanides,[11b] hydrolysis of the acylation product with the Katritzky reagent,[11c] (**20**) or addition of an organometallic[11d] intermediate to methyl chloroglyoxalate (Scheme 5). For introduction of the vicinal ketoester we chose the latter method due to compatibility with pyrazole functionality and convenient availability of dimethyl oxalate. Therefore the acetylene parent (**8a**) was lithiated at -70 ˚C with *n*-butyllithium in THF with subsequent warming to -60 ˚C and addition of dimethyl oxalate to quench the lithiated pyrazole. The subsequent product (**9a**) was isolated in 95.6 % yield after routine workup via water quench, followed by extraction and column chromatography. In the case of the unsubstituted 2*H*-pyrazole (**8b**), lithiation occurred regioselectively adjacent to the *N*-1-methyl group to give (**9b**) in 62 % yield. These compounds (**9a, 9b**) are representative of other substituted benzene analogs (X = 4-fluoro; 2,5-dimethyl; 2,5-dichloro; or 4-trifluoromethyl) that were synthesized and subsequently tested in our biological screen. These compounds (**9a, b**) displayed auxin symptomology in a wide variety of plant species which is similar to those reported by other known herbicides.[12] Plant species that were most affected were *Solanum, Abutilon, Amaranthus, Chenopodium, Galium, Ipomoea and Solanum*. These plants showed typically twisting and distorted growth of leaf tips and shoots.

CONCLUSION

The foregoing synthetic methodology shows the general versatility of pyrazole modifications using Sonogashira coupling reactions. The first stage efficiently makes use of the Sonogashira conditions to couple arylhalides to an acetylene precursor in 69-90 % yields. A second stage retro-Favorskii liberates phenyl acetylenes for coupling to iodopyrazoles in 65-85 %. Large scale application proved to have broad compatibility with functionality for further synthetic elaborations. Moreover, phase-transfer alkylation conditions gave efficient iodopyrazoles used in this scaled-up process. Although this methodology fails to employ an optimal one-pot-two-step-coupling strategy, this application to other heterocycles certainly can be expected to be a useful strategy for production of bis-heteroaryl-pyrazolylacetylenes and bis-pyrazolyl-pyrazolylacetylenes.

EXPERIMENTAL

Melting points were determined with MRK MEL-TEMP II and are uncorrected. The ^{1}H-NMR spectra were taken with JEOL JNM-GSX 270 spectrometer. Chemical shifts are reported in reference to tetramethylsilane as internal standard. GC analyses were carried out on a Varian 3300 gas chromatograph. Flash column chromatography was performed on E. Merck silica gel 60 (70-230 mesh or 230-400 mesh).

General coupling procedure for preparation of 3-trifluoromethylphenylacetylene (3a).

After stirring a solution of copper (I) iodide (120 mg, 0.63 mmol), triphenylphosphine (120 mg, 0.46 mmol) and bis-triphenylphosphine palladium dichloride (120 mg, 0.17 mmol) in diisopropylamine (140 mL) under argon atmosphere for 5 min, a mixture of 3-iodotrifluoromethylbenzene (**5a**) (50.7 g, 0.18 mol) and 1,1-dimethyl-2-propyn-1-ol (**7a**) (27 g, 0.32 mol) was added which resulted in exothermic

warming to 70 ˚C. The reaction temperature was increased and maintained at 80 ˚C. Monitor by GC showed the reaction completes within 1 h. The cooled reaction mixture was partitioned between EtOAc and water and dried (anhydrous Na_2SO_4). Evaporation of the excess solvent gave an oil which was combined with solid sodium hydroxide (3 g powdered pellets) and heating to 160 ˚C gave distillation of acetone with formation of acetylene product (**3a**) which was distilled at 140 ˚C under slight vacuum (30 Torr) to give 18.3 g (59 % yield) (**3a**). ^{1}H-NMR: ($CDCl_3$) 7.40-7.79 (m, 4H), 3.15 (s, 1H).

General coupling procedure for the preparation of 1,3-dimethyl-4-(3-trifluoromethyl-phenylethynyl)-1*H*-pyrazole (**8a**).

A typical procedure involves combining the triphenylphosphine (120 mg, 0.46 mmol), copper (I) iodide (120 mg, 0.63 mmol) and bis-triphenylphosphine palladium dichloride (120 mg, 0.17 mmol) catalyst in diisopropylamine (100 mL) with stirring under argon atmosphere for 5 min at rt. The pyrazolyl iodide (**14a**) (12 g, 0.054 mol) and phenylacetylene (**3a**) (9.8 g, 0.057 mol) were added and the mixture warmed to 80-85 ˚C. Monitor by GC showed the reaction completes within 3 h. The cooled solution was filtered from iodide salts and the mixture partitioned between EtOAc and 2N HCl, followed by washing with saturated aqueous $NaHCO_3$. After drying of the organic layer (anhydrous Na_2SO_4) the solvent was removed in-vacuo to give a residual oil which was chromatographed on silica gel. Isolated yield of (**8a**), 11.7 g (82 %). ^{1}H.NMR: ($CDCl_3$) 7.80-7.20 (m, 5H), 3.85, (s, 3H), 3.35 (s, 3H). Anal. Calcd for $C_{14}H_{11}F_3N_2$: C, 63.63; H, 4.20; N, 10.60. Found: C, 62.21, H, 4.03; N, 11.03.

Preparation of 2-methyl-4-(3-trifluoromethylphenylethynyl)-2*H*-pyrazole (**8b**).

By the general procedure above reaction of pyrazolyliodide (**16**) (44 g, 0.21 mol) and phenylacetylene (**3a**) (46.8 g, 0.27 mol) gave 35.5 g (67 %) (**8b**) after chromatography. ^{1}H-NMR: ($CDCl_3$) 7.75-7.40 (m, 6H), 3.95 (s, 3H). Anal. Calcd for $C_{13}H_9F_3N_2$: C, 62.40; H, 3.63; N, 11.20. Found: C, 62.20; H, 3.63; N, 11.13.

General lithiation procedure for preparation of [2,5-dimethyl-4-(3-trifluoromethylphenylethynyl)-2*H*-pyrazol-3-yl]-α-oxoacetic acid methyl ester (**9a**).

A typical procedure involved addition of *n*-butyllithium (60 mL, 1.6 M *n*-hexane soln., 0.096 mol) at -70 ˚C to a solution of the pyrazole (**8a**) (23 g, 0.087 mol) in THF (120 mL) with mechanical stirring continued for 90 min. Then a solution of dimethyl oxalate (31 g, 0.26 mol) in THF (120 mL) was added all at once at -60 ˚C. The temperature rose to -30 ˚C with continued stirring. The reaction was allowed to warm to rt overnight (12-15 h). The reaction was then quenched with water (50 mL) followed by partition between Et_2O and water and drying the organic phase (anhydrous Na_2SO_4). Chromatography of the residual oil after evaporation of solvent on silica gel gave an isolated yield of 29.2g, (95.6 %) of **9a**, mp 66 ˚C. ^{1}H-NMR: ($CDCl_3$) 7.45-7.80 (m, 4H), 4.15 (s, 3H), 3,85 (s, 3H), 2.40 (s, 3H). Anal. Calcd for $C_{17}H_{13}F_3N_2O_3$: C, 58.29; H, 3.74; N, 8.00. Found: C, 58.61; H, 3.34; N, 8.33.

Preparation of [2-methyl-4-(3-trifluoromethylphenylethynyl)-2*H*-pyrazol-3-yl]-α-oxoacetic acid methyl ester (**9b).**

By the general lithiation procedure above the reaction of pyrazole (**8b**) (9.5 g, 0.038 mol) gave similarly a

yield of 8 g (62 %) of **9b,** mp 79 ˚C. ^{1}H-NMR: ($CDCl_3$) 7.78-7.41 (m, 5H), 4.21 (s, 3H), 3.88 (s, 1H). Anal. Calcd for $C_{16}H_{11}F_3N_2O_3$: C, 57.15; H, 3.30; N, 8.33. Found: C, 58.01; H, 3.34; N, 8.23.

General condensation procedure for preparation of 3-methyl-1*H*-pyrazole (**11**).

To 3-oxobutyraldehyde dimethyl acetal (**10a**) (132 g, 1.0 mol) was added hydrazine hydrate (210 mL, 24 % soln., 1.0 mol,) with cooling maintained at 10 ˚C. Then acetic acid (60 mL) was slowly added allowing the temperature to rise to 30 ˚C. After complete addition, the bath temperature was adjusted to 85 ˚C for 1.5 h until the reaction was judged completed as monitored by GC. Removal of low boiling components by rotary evaporation followed by vacuum distillation of the residue through a Vigreux column gave the main fractions (85-100 ˚C / 30 Torr) corresponding to an unresolved mixture of pyrazole tautomers (**11**) 73 g, (60 % yield). ^{1}H-NMR: ($CDCl_3$) 8.20 (br s, 1H), 7.49 (s, 1H), 6.10 (s, 1H), 2.35 (s, 3H).

Preparation of 1*H*-pyrazole (**12**)**.**

By the general condensation procedure above, treatment of 1,1,3,3-tetramethoxypropane (**10b)** (220 g, 1.0 mol) with hydrazine hydrate (210 mL 24 % soln., 1.0 mol) and acetic acid (240 mL) gave a 90 % yield of **12**. ^{1}H-NMR: ($CDCl_3$) 8.20 (br s, 1H), 7.50 (s, 1H), 6.10 (s, 1H).

General iodination procedure for preparation of 4-iodo-3-methyl-1*H*-pyrazole (**13a) and 3-iodo-2-methyl-1*H*-pyrazole (13b**).

The pyrazole (**11**) (105 g, 1.20 mol) was dissolved in acetic acid (240 mL), CCl_4 (100 mL), iodine (145 g, 0.29 mol) and water (240 mL) containing iodic acid (45 g, 0.24 mol). The two-phase mixture was stirred vigorously which gave exothermic warming to 50 ˚C. The reaction was completed by GC monitor after 90 min. Sodium bisulfite (aq) (100 mL, 1 M soln.) was added to decolorize the solution followed by addition of NaOH (aq) (340 mL, 50 % soln.) to basify. The granular salt mixture was removed by filtration and the liquid filtrate extracted with EtOAc (2 x 500 mL). Drying of the organic layers over anhydrous Na_2SO_4 followed by filtration and evaporation gave (**13a, b**) as an amorphous solid mixture, 216 g, (81 % yield), mp 112 ˚C. ^{1}H-NMR: ($CDCl_3$) 7.50 (s, 1H), 7.40 (s, 1H), 2.35 (2 x s, 3H)

General phase-transfer-alkylation procedure for preparation of 4-iodo-1,3-dimethyl-1*H*-pyrazole (**14a) and 4-iodo-1,5-dimethyl-1*H*-pyrazole (14b**).

The pyrazole mixture of isomers (**13a, 13b**) (215 g, 1.03 mol) were dissolved in CH_2Cl_2 (1 L) containing tetra-*n*-butylammonium hydrogen sulfate (0.10 mol), NaOH (aq) (500 mL, 2 M soln.) and dimethyl sulfate (141 g, 1.12 mol). Vigorous stirring at rt showed after exothermic reaction two resolved product peaks by GC. The organic phase was separated and washed with brine and dried (anhydrous Na_2SO_4). The solvent after filtration was then evaporated to an oil which was stirred with *n*-hexane and decanted from the insoluble portion. The pyrazole fractions were concentrated after several extractions to give pyrazole (**14a),** 57.8 g, (26 %), ^{1}H-NMR: ($CDCl_3$) 7.40 (s, 1H), 3.85 (s, 3H), 2.30 (s, 3H) and (**14b**), 55.8 g, (24 %) yield. ^{1}H-NMR: ($CDCl_3$) 7.60 (s,1H), 3.95 (s, 3H).

Preparation of 1-methyl-1*H*-pyrazole (**15**)**.**

By the general phase-transfer procedure above for (**14a,b**) the reaction of pyrazole (**12**) gave 53 % yield

of (**15**). ^{1}H-NMR: ($CDCl_3$) 8.20 (br s, 1H), 7.60 (s, 1H), 7.50 (s, 1H), 3.90 (s, 3H).

Preparation of 4-iodo-1-methyl-1*H*-pyrazole (16).

By the general iodination procedure above for (**13a,b**) the reaction of pyrazole (**15**) (34.9 g, 0.43 mol) gave 44.1 g, 99 % yield of (**16**), mp 57 ˚C. ^{1}H-NMR: ($CDCl_3$) 7.62 (s, 1H), 7.50 (s, 1H), 3.92 (s, 3H).

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