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Novel application of the palladium-catalyzed *N*-arylation of hydrazones to a versatile new synthesis of pyrazoles

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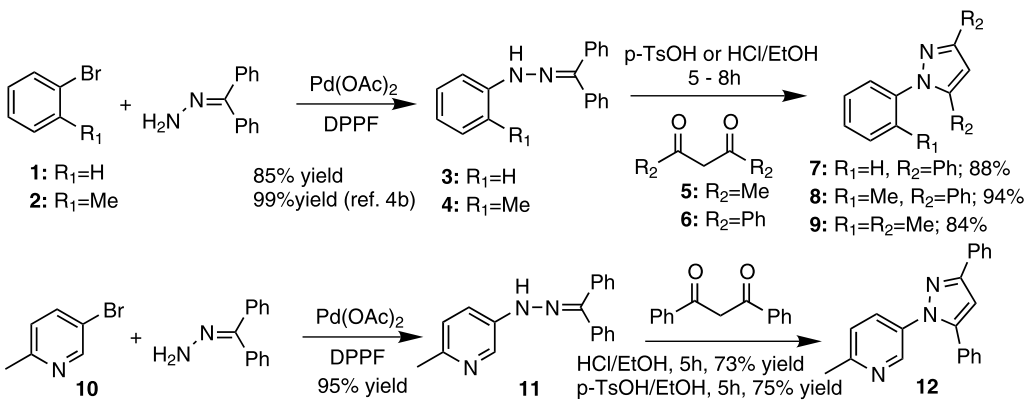
Abstract—A versatile synthesis of pyrazoles from aryl benzophenone hydrazones was demonstrated with a variety of 1,3-bifunctional substrates under acidic conditions. The obtained regioselectivity is consistent with transhydrazonation followed by subsequent cyclization. © 2002 Elsevier Science Ltd. All rights reserved.

Aryl pyrazoles posses a widespread occurrence as substructures in a large variety of compounds with important biological activities and pharmacological properties.[1,2] The synthesis of this important family of compounds is well reviewed.[2] The conventional approach for pyrazole formation based on condensation of substituted hydrazines with 1,3-diketones or their equivalents, such as β-ketoesters and β-cyanoketones. With the limitation associated with availability of differently substituted aryl- and hetero-aryl hydrazines,[3] it became attractive to develop a one-pot synthesis of pyrazoles from *N*-arylated benzophenone hydrazones, which could easily be prepared following Buchwald[4a] and Hartwig[4b] procedures. We postulated that upon treatment of arylhydrazones with dicarbonyl compounds, a transhydrazonation reaction[4a] followed by subsequent cyclization would take place, leading eventually to pyrazoles.

Hydrazones **3**, **4** and **11**, were prepared in high yields, following Hartwig's procedure[4b] for the preparation of **4**. The synthesis of aryl pyrazoles was first examined by refluxing **3**, **4** and **11** with symmetrical 1,3-diketones **5** or **6** in ethanol under different acidic conditions (HCl, AcOH, TFA, NH_4Cl, *p*-TsOH) (Scheme 1). The best yields were obtained by using *p*-TsOH or HCl in ethanol under reflux conditions for ca. 5–8 h. Pyrazoles **8**, **9** and **12** were obtained in 75–94% isolated yields[5] under *p*-TsOH/EtOH conditions. Similar yields were obtained in preparing pyrazoles **7** and **12** under HCl/EtOH conditions.[6]



Scheme 1.

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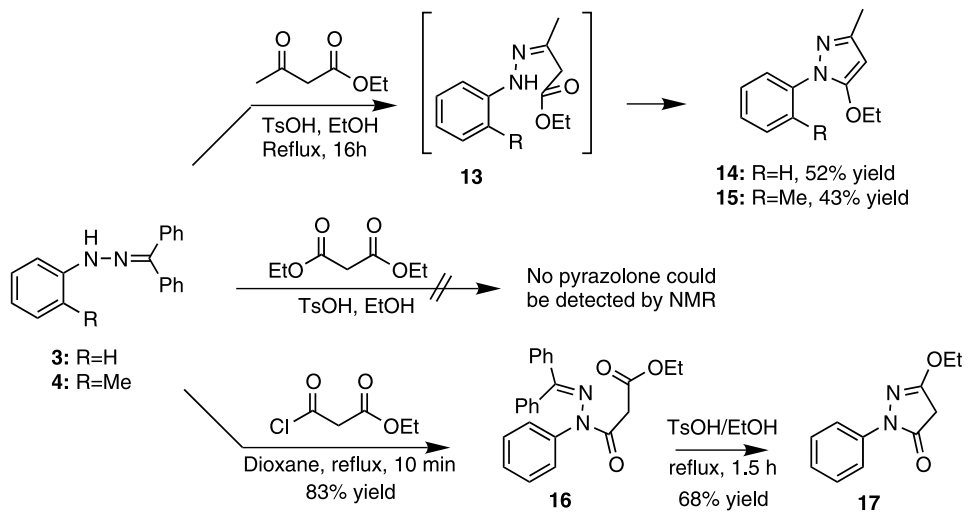
The results obtained with symmetrical diketones prompted us to examine the regioselective synthesis of unsymmetrical pyrazoles or pyrazole-related structures. Treatment of **3** and **4** with ethyl acetoacetate, under *p*-TsOH/EtOH conditions, has provided pyrazoles **14** and **15**, respectively in 52 and 43% isolated yield (Scheme 2).[7] The products are consistent with the transhydrazonation intermediate **13**. Attempts for the synthesis of pyrazolones upon treatment of hydrazone **4** with diethyl malonate under the *p*-TsOH reaction conditions were not successful. No pyrazolone formation was obtained and most of hydrazone **4** was recovered after 52 h. However, the poor reactivity of 1,3-diesters was overcome by treatment of **3** with ethyl malonyl chloride in refluxing dioxane, affording after 10 min the corresponding compound **16** in 80–83% isolated yield. Subsequent cyclization of **16** in *p*-TsOH/EtOH afforded, after 1.5 h, pyrazolone **17** in 70% yield. The ^{1}H NMR of compound **17** was found in full agreement with previously reported data.[8]

Preparation of pyrazole amines was expected to be possible by treating hydrazones with cyanoketone **18** under acidic conditions. Regioselective transhydrazonation could be expected to be similar to that obtained with β-ketoesters which then will provide pyrazole amines of type **19** (Scheme 3). Indeed, treatment of aryl hydrazones **3** with pivaloylacetonitrile (**18**) afforded single products **19** in 80% isolated yield. The structure of **19** was confirmed by its preparation from phenylhydrazine (**21**) with **18** under similar reaction conditions.

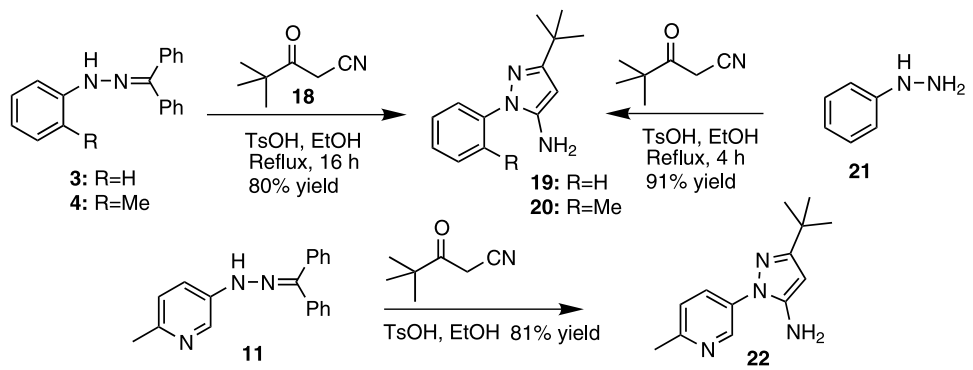
The utility of the cross-coupling/pyrazole formation sequence was further demonstrated in the synthesis of heteroaryl pyrazole **22** in 81% isolated yield.

In order to examine the regioselectivity of pyrazole formation with unsymmetrical diketones, hydrazone **3** was treated with 1-benzoylacetone under the typical conditions.[6] A mixture of 3-methyl-1,5-diphenylpyrazole (**23**) and 5-methyl-1,3-diphenylpyrazole (**24**) was obtained in 5:1 ratio, respectively in 82% total yield (Scheme 4). However, 22:1 ratio of **23** versus **24** was obtained on their preparation from hydrazine **21** and 1-benzoylacetone.[5] Higher regioselectivity was expected in the pyrazole formation from 2,2-dimethyl-3,5-hexanedione. Indeed, single products **25** and **26** were obtained upon its reaction under the *p*-TsOH/EtOH conditions with hydrazones **4** and **11** in 84 and 88% yields, respectively.[9]

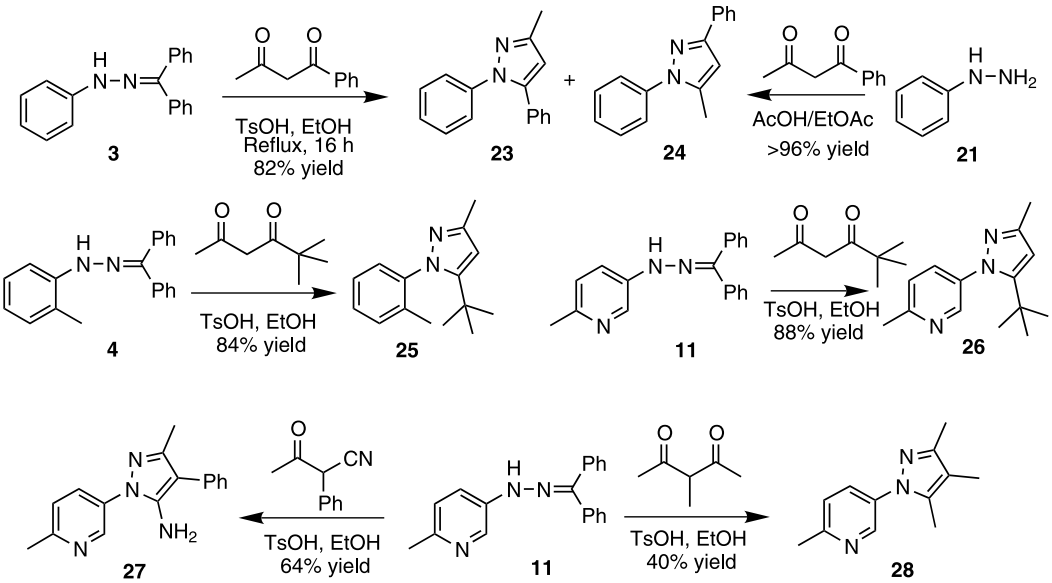
Preparation of tetra-substituted pyrazoles from hydrazone **11** with α-acetylphenylacetonitrile and 3-methyl-2,4-pentanedione was examined under the developed conditions and provided pyrazoles **27** and **28** in 40 and 64% isolated yields, respectively.



Scheme 2.



Scheme 3.



Scheme 4.

In summary, variety of pyrazoles and pyrazolones could be prepared, under the developed conditions, from easily accessible aryl and heteroaryl benzophenone hydrazones with different 1,3-bifunctional groups.

Acknowledgements

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References

1. (a) Pargellis, C.; Tong, L.; Churchill, L.; Cirillo, P.; Gilmore, G.; Graham, A. G.; Grob, P. A.; Hickey, E. R.; Moss, N.; Pav, S.; Regan, J. *Nature Struct. Biol.*, in press; (b) Dumas, J.; Hatoum-Mokdad, H.; Sibley, R.; Riedl, B.; Scott, W. J.; Monahan, M. K.; Lowinger, T. B.; Brennan, C.; Natero, R.; Turner, T.; Johnson, J.; Schoenleber, R.; Bhargava, A.; Wilhelm, S. W.; Housley, T. J.; Gerald, E. R.; Shrikhande, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2051; (c) Menozzi, G.; Mosti, L.; Schenone, P.; Donnoli, D.; Schiariti, F.; Marmo, E. *Farmaco* **1990**, *45*, 167.
2. On the synthesis of pyrazoles and pyrazole related structures see: (a) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocyclic Chem.* **1998**, *35*, 489; (b) Elguero, J. *Compr. Heterocyclic Chem. II* **1996**, *3*, 1; (c) Takagi, K.; Huber-Habart, M. *J. Heterocyclic Chem.* **1996**, *33*, 1003; (d) El-Rayyes, N. R.; Al-Awadi, N. A. *Synthesis* **1985**, 1028; (e) Sammes, M. P.; Katritzky, A. R. *Advances in Heterocyclic Chemistry*, Vol. 34, Academic Press, **1983**; (g) Behr, L. C.; Fusco, R.; Jarboe, C. H. *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed., Interscience Publishers: John Wiley and Sons, **1967**.
3. For palladium-catalyzed coupling of *t*-butylcarbazate with activated aryl bromides, see: Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543.
4. (a) Wagaw, S.; Yang, H. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621; (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2090.
5. All new compounds were characterized by full spectroscopic data, yields refer to chromatographed materials with purity of >95%. Structure of **7** found in agreement with previously reported data: Texier-Boullet, F.; Klein, B.; Hamelin, J. *Synthesis* **1986**, 409.
6. **Typical procedure**:
Solution of the benzophenone hydrazone (1.75 mmol), *p*-TsOH (or conc. HCl) (8.75 mmol) and the bi-functional substrate (2.63 mmol) in EtOH (10 mL) was refluxed for a period of 8–16 h. The reaction mixture was cooled to rt, then $NaHCO_3$ saturated solution (10 mL) and EtOAc (10 mL) were added. The layers were separated, and the aqueous layer washed with EtOAc. The combined organics dried (Na_2SO_4), concentrated then purified by column chromatography.
7. Selected ^{1}H NMR data from **14**: δ 5.47 (1H, s), 4.12 (2H, q), 2.28 (3H, s), 1.43 (3H, t) (in full agreement with reported data: Katritzky, A. R.; Main, F. W. *Tetrahedron* **1964**, *20*, 299). Compound **15**: δ 5.44 (1H, s), 4.07 (2H, q), 2.26 (3H, s), 1.33 (3H, t).
8. Selected ^{1}H NMR data from **17**: δ 4.35 (2H, q), 3.48 (1H, s) (in full agreement with literature; Molinari, A.; Oliva, A. *J. Heterocyclic Chem.* **1996**, *33*, 479.)
9. NOESY experiments indicate NOE between the aryl-rings and the *t*-butyl substituents and absence of NOE with the methyl substituent on the pyrazole rings in structures **25** and **26**. These results are consistent with the expected regioselectivity.