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Microwave-assisted synthesis utilizing supported reagents: a rapid and versatile synthesis of 1,5-diarylpyrazoles

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Abstract—The application of microwave heating to a silica-assisted solution-phase synthesis technique has been utilized to develop a rapid and efficient two-step protocol for the preparation of pyrazoles from aryl methyl ketone and aryl hydrazine monomers.

The utilization of supported reagents for the solution-phase synthesis of both singletons and libraries has become an increasingly applied tool for the preparation of molecules of biological interest.[1] One reason for this escalation emanates from the appreciation that this technology provides a beneficial method of performing chemical transformations with minimal workup. Moreover, an ever-expanding collection of commercially available supported reagents, for both synthesis and purification,[2] renders this technology more accessible.

In a parallel medicinal chemistry (PMC) environment this technology is appealing since excess amounts of reagents can be used to drive reactions to completion. This culminates in the production of libraries of higher purity, which is advantageous for the development of rapid SAR in medicinal chemistry programs. This is also advantageous when subsequent modification or additional purification is required. In addition, when using supported reagents reactions can be easily monitored by conventional methods.

Aryl pyrazoles are ubiquitous substructures within a diverse array of compounds with important biological activity and pharmacological properties.[3] The synthesis of this eminent family of compounds has been well reviewed.[4] The conventional approach for pyrazole formation is based on the condensation of substituted hydrazines with 1,3-diketones or their equivalents, such as β-ketoesters and β-cyanoketones. Limitations to this approach are associated with scarce availability of diversely substituted 1,3-diketones. As an alternative, it became appealing to develop a two-step synthesis of pyrazoles from aryl methyl ketones and aryl hydrazines.[5]

The reaction of 4-methylacetophenone **1** with ethyl trifluoroacetate **2** was carried out under a variety of conditions (Table 1).[5–7] The highest yielding non-microwave conditions (entry 2) took 5 days to reach completion. Elevated temperatures (entry 3) decreased the reaction time to 2 h, although the yield was compromised. On transferring these conditions into the microwave, the desired enol ketone **3** was afforded in 10 min with an excellent yield (entry 4).[8,9]

With an efficient method to prepare enol ketone **3** in hand, optimization of the next step was undertaken. Reaction of enol ketone **3** with 4-methylphenylhydrazine **4** was carried out under a variety of conditions (Table 2).[5,7] Firstly, the use of *para*-toluenesulfonic acid in ethanol was attempted under non-microwave conditions (100 °C), with an excellent yield being obtained in 7 h (entry 1). When these conditions were attempted in the microwave (160 °C) a 61% yield of pyrazole **5** was obtained (entry 2). On changing the acid source to silica-supported toluenesulfonic acid,[10] excellent yields were obtained in both the thermal and microwave cases (entries 3 and 4).

Keywords: Pyrazole; Aryl methyl ketone; Aryl hydrazine; Silica-supported reagent; Microwave.
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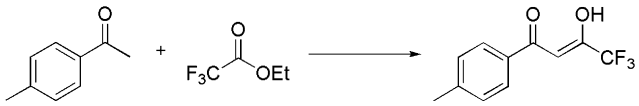
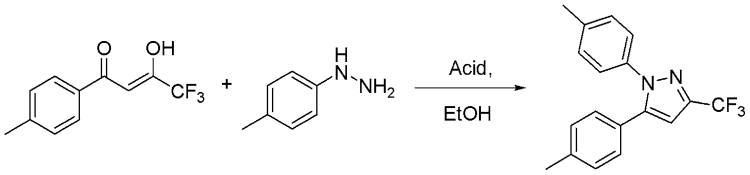
Table 1. Effect of microwave heating on the reaction between 4-methylacetophenone **1** and ethyl trifluoroacetate **2**



1 **2** **3**

Entry	Base	Solvent	Method	Temp (°C)	Time	Yield (%)
1	NaOMe	MTBE	Non-microwave	25	14 h	25
2	NaH	DMF	Non-microwave	25	5 days	88
3	NaH	DME	Non-microwave	100	2 h	60
4	NaH	DME	Microwave	160	10 min	95

Table 2. Effect of microwave heating and silica-supported acid source on the reaction between enol ketone **3** and 4-methylphenylhydrazine **4**



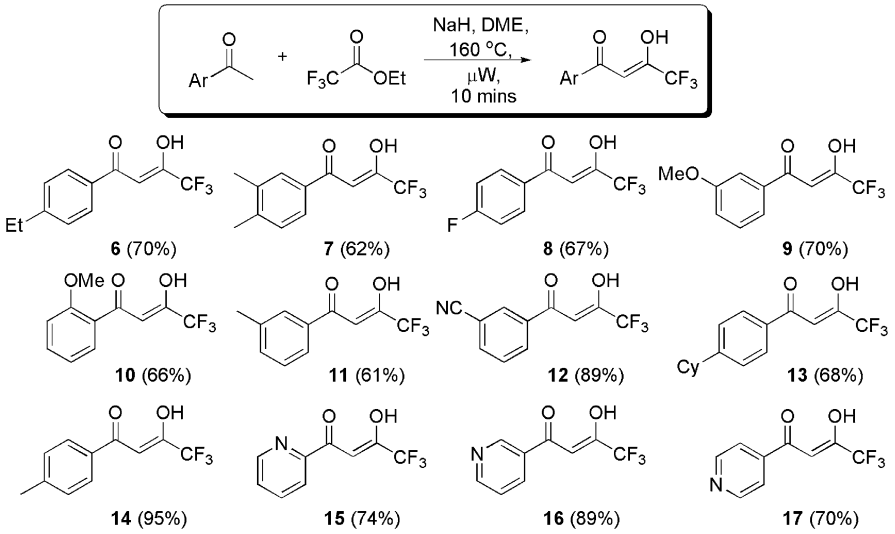
3 **4** **5**

Entry	Acid	Method	Temp (°C)	Time	Yield (%)
1	*p*TsOH	Non-microwave	100	7 h	95
2	*p*TsOH	Microwave	160	5 min	61
3	Si-TsOH	Non-microwave	100	6 h	84
4	Si-TsOH	Microwave	160	5 min	95

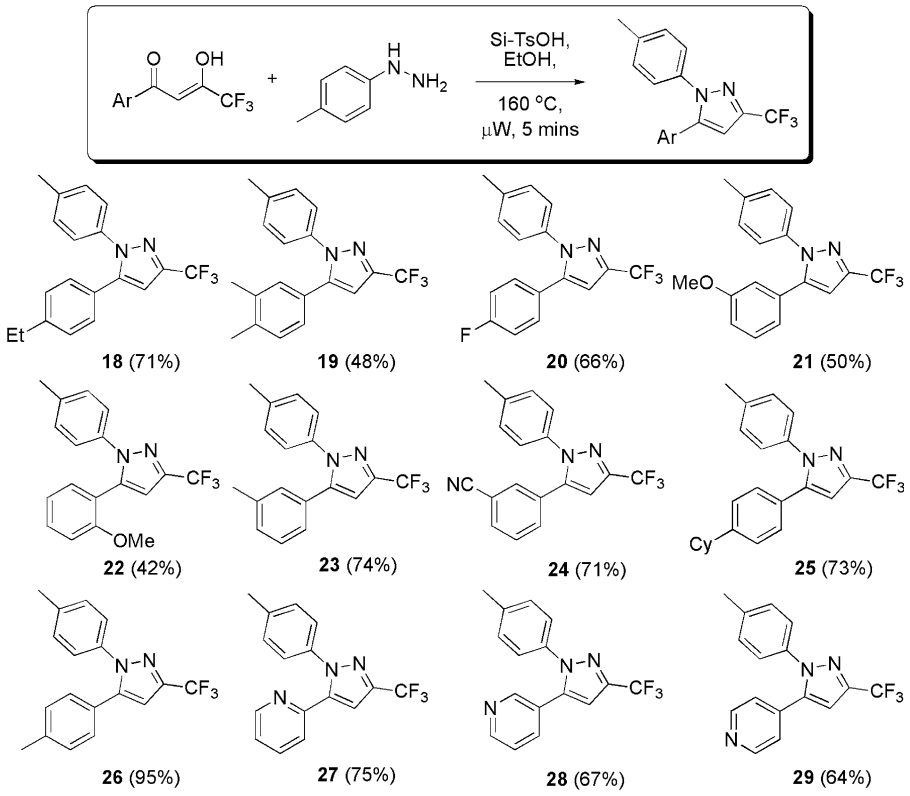
When using the silica-supported reagent no work-up was performed. The crude reaction mixture was evaporated to dryness, and the resulting free flowing solid purified directly by flash column chromatography.[11] The optimum conditions for this reaction (entry 4) yielded pyrazole **5** in 95% yield in 5 min.[12]

With the above results in hand, we then pursued a variety of targets by performing the microwave-assisted enolate reaction followed by the microwave-assisted hydrazine addition to the resulting intermediates. Schemes 1 and 2 highlight the efficiency of this approach toward the synthesis of pyrazole analogues.[13]

In summary, we have described a rapid, convenient, and high-yielding two-step protocol for the preparation of pyrazoles. The procedure utilizes commercially available reagents and equipment that are suitable for the preparation of singletons or automated library production.



Scheme 1. Targets accessed by microwave-assisted enolate formation.



Scheme 2. Targets accessed by microwave-assisted pyrazole formation.

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References and notes

1. For recent examples see: (a) Senten, K.; Danieels, L.; Van der Veken, P.; De Meester, I.; Lambeir, A.-M.; Scharpe, S.; Haemers, A.; Augustyns, K. *J. Comb. Chem.* **2003**, *5*, 336–344; (b) South, M. S.; Dice, T. A.; Girard, T. J.; Lachance, R. M.; Stevens, A. M.; Stegeman, R. A.; Stallings, W. C.; Kurumbail, R. G.; Parlow, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2363–2367; (c) South, M. S.; Case, B. L.; Wood, R. S.; Jones, D. E.; Hayes, M. J.; Girard, T. J.; Lachance, R. M.; Nicholson, N. S.; Clare, M.; Stevens, A. M.; Stegeman, R. A.; Stallings, W. C.; Kurumbail, R. G.; Parlow, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2319–2325; (d) Jaunzems, J.; Hofer, E.; Jesberger, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1166–1170; (e) Vickerstaffe, E.; Warrington, B. H.; Ladlow, M.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 2419–2422; (f) Sauer, D. R.; Kalvin, D.; Phelan, K. M. *Org. Lett.* **2003**, *5*, 4721–4724.
2. (a) Flynn, D. L.; Devraj, R. V.; Naing, W.; Parlow, J. J.; Weidner, J. J.; Yang, S. *Med. Chem. Res.* **1998**, *8*, 219–243; (b) Flynn, D. L.; Devraj, R. V.; Parlow, J. J. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 41–50; (c) Weidner, J. J.; Parlow, J. J.; Flynn, D. L. *Tetrahedron Lett.* **1999**, *40*, 239–242.
3. (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.* **2002**, *9*, 268–272; (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*, 2051–2054; (c) Menozzi, G.; Mosti, L.; Schenone, P.; Donnoli, D.; Schiariti, F.; Marmo, E. *Farmaco* **1990**, *45*, 167–186.
4. On the synthesis of pyrazoles and pyrazole related structures see: (a) Hadad, N.; Baron, J. *Tetrahedron Lett.* **2002**, *43*, 2171–2173; (b) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1998**, *35*, 489–497; (c) Elguero, J. *Compr. Heterocycl. Chem. II* **1996**, *3*, 1–75; (d) Takagi, K.; Hubert-Habart, M. *J. Heterocycl. Chem.* **1996**, *33*, 1003–1015; (e) El-Rayyes, N. R.; Al-Awadi, N. A. *Synthesis* **1985**, 1028–1042; (f) Sammes, M. P.; Katritzky, A. R. In *Advances in Heterocyclic Chemistry*; Academic Press, 1983; Vol. 34; (g) Behr, L. C.; Fusco, R.; Jarboe, C. H. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.; Interscience Publishers, John Wiley and Sons, 1967.
5. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Andreson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365.
6. Baxter, A. J. G.; Fuher, J.; Teague, S. J. *Synthesis* **1994**, 207–211.
7. All microwave-assisted reactions were performed on either a Biotage Emrys Creator or a Biotage Smith Synthesizer (http://www.biotage.com).

8. All new compounds were characterized by full spectroscopic data, yields refer to chromatographed materials with purity of >95%.
9. *General procedure for the preparation of enol ketones*. A Smith Process Vial (2–5 mL) was charged with a stir bar, sodium hydride (60% dispersion in mineral oil, 10 mmol), and dimethoxyethane (5 mL). To this solution was added ethyl trifluoroacetate **2** (10 mmol) and 4-methylacetophenone **1** (5 mmol) dropwise. The reaction vessel was sealed and heated at 160 °C for 10 min (fixed hold time) in a Biotage Emrys Creator. After cooling, the vessel was uncapped and the reaction mixture quenched with 2 M aqueous hydrochloric acid (10 mL). This solution was then extracted with diethyl ether (3×10 mL) and the combined organic extracts dried (anhydrous magnesium sulfate), filtered, and concentrated in vacuo. Purification (Biotage Sp4) by silica gel chromatography (hexanes to ethyl acetate over 10 column volumes) afforded **3** (1.09 g, 95%) as an orange solid.
10. SiliCycle, Inc., http://www.silicycle.com.
11. All purifications were performed on either a Biotage Sp1 or a Biotage Sp4 (http://www.biotage.com).
12. *General procedure for the preparation of pyrazoles*. A Smith Process Vial (2–5 mL) was charged with a stir bar, enol ketone **3** (0.45 mmol), and ethanol (5 mL). To this solution was added Si-toluenesulfonic acid (1.5 mmol) and 4-methylphenylhydrazine **4** (0.3 mmol). The reaction vessel was sealed and heated at 160 °C for 5 min (fixed hold time) in a Biotage Emrys Creator. After cooling, the vessel was uncapped and the reaction mixture concentrated in vacuo. Purification (Biotage Sp4) by silica gel chromatography (hexanes to ethyl acetate over 10 column volumes) afforded **5** (0.09 g, 95%) as a yellow solid.
13. Although this work was performed in the 2–5 mL Smith Process Vials, we see no reason why this chemistry cannot be performed in the other Biotage vial formats. This will presumably facilitate both library synthesis and scale-up chemistry.