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$Sc(OTf)_3$-catalyzed, solvent-free domino synthesis of functionalized pyrazoles under controlled microwave irradiation

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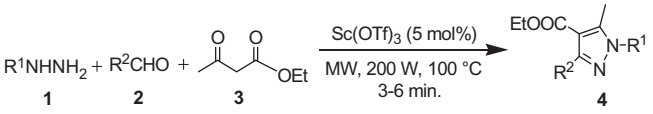
ABSTRACT

An efficient, rapid, and green synthesis of functionalized pyrazoles has been accomplished under solvent-free conditions by the reaction of phenyl hydrazine, aldehydes and ethyl acetoacetate. This approach exploits the synthetic potential of microwave irradiation and scandium triflate combination and offers many advantages such as excellent product yields, shorter reaction time, easy isolation of products, and environmentally benign reaction conditions.

Green chemistry has come to the forefront of current chemical research to develop efficient, sustainable, and environmentally benign synthetic methodologies.[1,2] Multicomponent reactions (MCRs) have been recognized as a powerful tool for the expedient creation of chemical libraries of drug-like compounds with high levels of molecular complexity and diversity.[3,4] Applicability of focused microwave assisted organic synthesis (MAOS) is nowadays practiced for rapid and reliable production of chemical entities.[5] Thus, multicomponent procedures employing microwave (MW) irradiation under solvent-free conditions are particularly welcome due to their intrinsic advantages,[6] particularly under the present paradigm shift to green methodologies.

Transition metal catalyzed carbon–carbon and carbon–heteroatom bond formations via multicomponent reactions are of utmost importance in organic synthesis,[7] because of their high reactivity, selectivity, and mild reaction conditions. Of these, scandium triflate [$Sc(OTf)_3$] has emerged as a powerful Lewis acid catalyst to perform many useful organic transformations[8] under mild reaction conditions. Due to easy handling, stability to moisture, and reusability, $Sc(OTf)_3$ is expected to solve some severe environmental problems caused by mineral or Lewis acid promoted reactions in the chemical industry.

Heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. Therefore, the interest for developing new, versatile, and efficient synthesis of heterocycles has always been a thread in the synthetic community.[9] The pyrazole core is a privileged heterocyclic scaffold,[10] and is a constituent of agro-chemicals,[11] and polymeric materials,[12] besides its use as a unique ligand.[13] Although pyrazoles are rarely found in natural products, they represent an important motif of man-made biologically active compounds such as celecoxib, fipronil, lonazolac, viagra, and many others.[14]



Scheme 1. $Sc(OTf)_3$-catalyzed synthesis of functionalized pyrazoles.

The most popular methods for the preparation of fully substituted pyrazoles involve 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins,[15] the Knorr condensation of hydrazine with 1,3-dicarbonyl or their derivatives,[16] the cross coupling of 5-bromopyrazole derivatives with various nucleophiles or the sequential Suzuki coupling of pyrazole boronate derivatives using a metal directing group,[17] and by N-arylation of functionalized pyrazoles.[18] A one-pot synthesis of pyrazoles using $Yb(PFO)_3$ is also described under conventional conditions.[19] While these methods provide the synthetic chemists with a multitude of choices to construct substituted pyrazoles, almost all of them suffer from one or the other drawbacks such as regiochemical infidelity, multistep sequence, low product yield, or longer reaction time, which has limited the exploitation of these methods in high throughput

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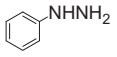
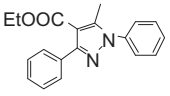
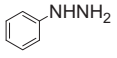
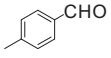
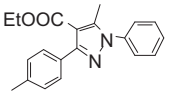
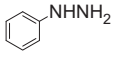
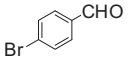
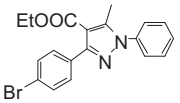
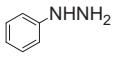
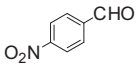
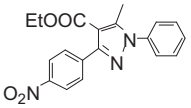
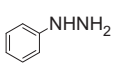
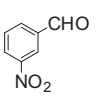
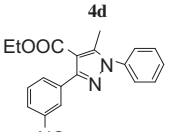
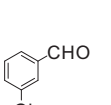
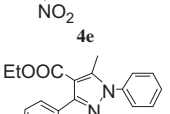
Table 1
Optimization of reaction conditions for the synthesis[a] of pyrazole **4a**

Entry	Catalyst (mol %)	Solvent	Conventional			Microwave			
			Temp (°C)	Time (min)	Yield[b] (%)	Temp (°C)	Power (Watt)	Time (min)	Yield[b] (%)
1	L-Proline (10)	—	100	180	nr[c]	100	200	8	Traces
2	Zn-(L-proline)$_2$ (10)	—	100	180	nr[c]	100	200	8	nr[c]
3	Guanidinium chloride (10)	—	100	180	nr[c]	100	200	8	nr[c]
4	CdI_2 (10)	—	100	120	51	100	200	8	60
5	*p*-TSA (10)	—	100	180	46	100	200	8	56
6	$Co(OAc)_2{\cdot}2H_2O$ (10)	—	100	180	12	100	200	8	24
7	$LiClO_4$ (10)	—	100	150	31	100	200	8	42
8	TiO_2 (10)	—	100	180	29	100	200	8	41
9	P_2O_5 (10)	—	100	120	59	100	200	8	67
10	$MnCl_2{\cdot}4H_2O$ (10)	—	100	180	Traces	100	200	8	19
11	Iodine (10)	—	100	120	54	100	200	8	65
12	$Fe(SO_4)_2{\cdot}9H_2O$ (10)	—	100	180	47	100	200	8	69
13	$Sc(OTf)_3$ (10)	—	100	75	73	100	200	5	84
14	**$Sc(OTf_3)$ (5)**	—	**100**	**75**	**74**	**100**	**200**	**5**	**84**
15	$Sc(OTf)_3$ (3)	—	100	75	70	100	200	5	71
16	$Sc(OTf)_3$ (5)	—	90	75	64	100	150	5	79
17	$Sc(OTf)_3$ (5)	—	120	75	74	100	250	5	84
18	$Sc(OTf)_3$ (5)	Toluene	100	75	63	100	200	5	72
19	$Sc(OTf)_3$ (5)	Chlorobenzene	100	75	65	100	200	5	73
20	$Sc(OTf)_3$ (5)	Ethanol	80	75	53	80	200	5	64
21	$Sc(OTf)_3$ (5)	Acetonitrile	80	75	60	80	200	5	69
22	$Sc(OTf)_3$ (5)	$[Bmim]BF_4$	100	75	55	100	200	5	65

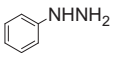
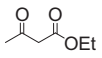
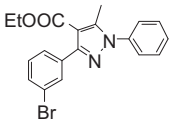
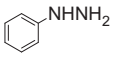
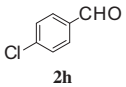
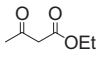
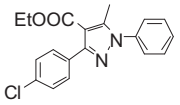
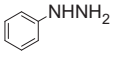
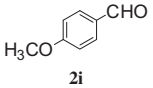
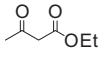
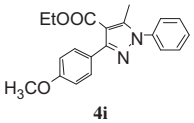
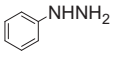
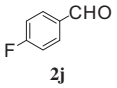
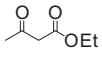
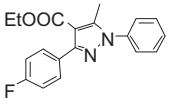
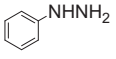
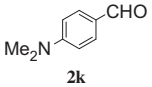
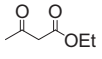
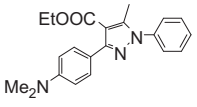
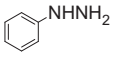
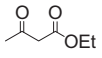
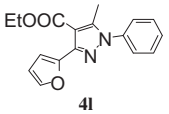
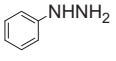
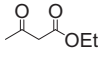
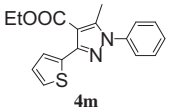
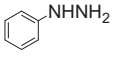
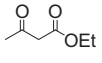
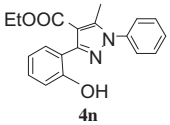
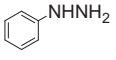
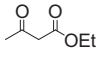
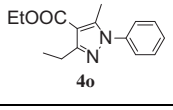
[a] Used phenyl hydrazine–aldehyde–ethyl acetoacetate (1:1:1.2).
[b] Isolated yield based on benzaldehyde.
[c] nr = no reaction.

Table 2
MW assisted one-pot synthesis[a] of pyrazoles using $Sc(OTf)_3$ as a catalyst

Entry	Reactants			Product	Time (min)	Yield[b] (%)
	1	2	3			
1		 **2a**		 **4a**	5	83
2		 **2b**		 **4b**	5	76
3		 **2c**		 **4c**	4	83
4		 **2d**		 **4d**	5	88
5		 **2e**		 **4e**	3	92
6		 **2f**		 **4f**	4	86

(*continued on next page*)

Table 2 (*continued*)

Entry	Reactants			Product	Time (min)	Yield[b] (%)
	1	2	3			
7		 **2g**		 **4g**	4	85
8		 **2h**		 **4h**	4	84
9		 **2i**		 **4i**	6	74
10		 **2j**		 **4j**	3	90
11		 **2k**		 **4k**	5	81
12		 **2l**		 **4l**	4	82
13		 **2m**		 **4m**	4	84
14		 **2n**		 **4n**	8	nr[c]
15		 **2o**		 **4o**	5	81

[a] Reaction conditions: Aldehyde (1 mmol), phenyl hydrazine (1 mmol), ethyl acetoacetate (1.2 mmol), 200 W MW power, 100 °C.
[b] Isolated yield based on aldehyde.
[c] nr = no reaction.

synthesis. Thus, an improved, efficient, and green alternative approach to functionalized pyrazoles is of current interest to organic chemists.

As part of our continued interest to develop efficient protocols for the synthesis of biologically active molecular scaffolds via one-pot multicomponent reactions,[20] we report herein an efficient use of $Sc(OTf)_3$ and microwave combination for a benign, rapid, and convenient synthesis of functionalized pyrazoles in excellent yields (74–92%) through the one-pot three-component reaction of phenyl hydrazine, aldehydes and ethyl acetoacetate under solvent-free conditions (Scheme 1).

The studies were initiated to optimize the reaction conditions for a model multicomponent reaction between phenyl hydrazine (**1**), benzaldehyde (**2a**), and ethyl acetoacetate (**3**). As solvent-free synthesis has gained much current interest, it was imperative to investigate the reaction under solvent-free conditions. In order to develop a viable approach, the model reaction was investigated by employing different catalysts both under conventional and microwave conditions and the overall findings are given in Table 1. Gratifyingly, it was found that the reaction gave promising results in the presence of $Sc(OTf)_3$ at 100 °C (Table 1, entry 13) both under conventional as well as microwave conditions. Due to advantages associated with organo-catalyzed reactions, an attempt was made to study the reaction with L-proline, Zn-(L-proline)$_2$ and guanidinium chloride, but no observable product was formed (Table 1, entries 1–3). The use of catalysts such as CdI_2, *p*-TSA, $LiClO_4$, TiO_2, P_2O_5, iodine and $Fe(SO_4)_2{\cdot}9H_2O$ also promoted the reaction to a considerable extent, but catalysts like $Co(OAc)_2{\cdot}2H_2O$ and $MnCl_2{\cdot}4H_2O$ (Table 1, entries 6 and 10) provided rather poor yields. In terms of catalyst concentration, 5 mol % of $Sc(OTf)_3$ was necessary and sufficient for the completion of model reaction (Table 1, entry 14), as the reaction remains incomplete when 3 mol % of cat-

alyst was used (Table 1, entry 15). In order to screen the effect of solvent and temperature, the model reaction was undertaken both under conventional and microwave conditions using 5 mol % of $Sc(OTf)_3$ in different solvents at varying temperatures. The optimum conversion was achieved under solvent-free conditions at 100 °C. The model reaction was also studied by varying microwave power (150, 200 and 250 W) and it was concluded that 200 W power output at 100 °C was needed to accomplish maximum conversion to product **4a**.

Under the optimized set of MW reaction conditions (5 mol % of $Sc(OTf)_3$, 200 W, 100 °C), a number of aldehydes **2** were subsequently allowed to react with phenyl hydrazine **1** and ethyl acetoacetate **3** to afford various pyrazole derivatives (**4a–4o**) in reasonably good to excellent yields in 3–6 min (Table 2).[21] Interestingly, aromatic aldehydes with electron withdrawing groups gave products with higher yields in comparison to those having electron donating groups. It is worth noting that the reaction with *o*-salicylaldehyde did not provide the expected product, and the reaction stopped at the condensation stage with no further reaction with ethyl acetoacetate. Heteroaromatic and aliphatic aldehydes such as furan-2-carboxaldehdye, thiophene-2-carboxaldehyde, and propionaldehyde also participated well in the reaction (Table 2, entries 12, 13 and 15).

After completion of the reaction, dichloromethane (DCM) was added to the reaction mixture and the catalyst was recovered by filtration. After washing with DCM and drying in air, the recovered catalyst was reused without any loss in its catalytic activity.

In conclusion, we have successfully developed a simple, green, and efficient microwave assisted one-pot multicomponent synthesis of pyrazole derivatives from easily available starting materials using $Sc(OTf)_3$ as a catalyst under solvent-free conditions. This protocol is attractive in terms of, atom economy, shortened reaction time, simple and clean reaction profiles, tolerance of various functional groups, and reusability of the catalyst.

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21. *Experimental procedure*: A mixture of appropriate aldehyde (1 mmol), phenyl hydrazine (1 mmol) and 5 mol % $Sc(OTf)_3$ was placed in a 10-mL pressurized vial and stirred for 5 min. To it was then added ethyl acetoacetate (1.2 mmol) and was put in the "snap-on" cap. The reaction contents were irradiated in a mono-mode CEM Discover microwave synthesis system using 200 W MW power at 100 °C for appropriate time. After completion of the reaction (as indicated by TLC), the mixture was cooled to rt and to it was added DCM and stirred. The catalyst was recovered by filtration. The filtrate was washed with satd aq brine solution, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1:10) to afford the pure product.