Accelerated Synthesis of Pyrazoles Mediated by Water Microdroplets

Manish Jana^{†a}, Keerthana Unni^{†b, a}, Prof. Thalappil Pradeep^{*b}, Prof. R. Graham Cooks^{*a}

^a Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

^b DST unit of Nanoscience (DST UNS) and Thematic unit of Excellence (TUE), Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India.

Email: cooks@purdue.edu, pradeep@iitm.ac.in

([†] These authors have contributed equally to this work)

Total number of pages: 23 (S1-S23)

Total number of figures: 28 (figure S1-S28)

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- 1. Additional Experimental Details
- **1.1. Collection Setup for Scale Up Experiment:**



Collection Setup for Scale Up

Figure S1. Schematic representation of the collection setup for scale up experiments.

1.2. Conversion Ratio Calculation.

Conversion ratios from a mass spectrum can be determined using the ion intensities of reactants, intermediates, and products, based on any of the following equations:

Conversion Ratio =
$$\frac{I_p}{I_p + I_R + I_{INT}} * 100 \%$$
 ------(1)
Conversion Ratio = $\frac{I_p}{I_p + I_R} * 100 \%$ ------(2)
Conversion Ratio = $\frac{I_p + I_{INT}}{I_p + I_R + I_{INT}} * 100 \%$ ------(3)

Where I_p , I_R and I_{INT} are the total ion intensity of the products, reactants and intermediates (respectively) formed during the reaction. In our case, we have used the first equation to determine the conversion ratio during the microdroplet reactions. This method represents the most stringent approach to calculating the conversion ratio, as it accounts for the ion intensity of the intermediates.

2. Microdroplet reaction of ethyl acetoacetate (1a) and phenyl hydrazine (2a).

133 a) b) 100 175 CID = 30 *m/z* 175 *m/z* 158 80 \cap R. A. (%) - HCEC-OH 175 60 CC ≈<mark>i</mark>ith 147 40 *m/z* 175 *m/z* 147 *m/z* 106 135 20 130 158 106 118 0 175 150 200 75 100 125 m/z *m/z* 133 *m/z* 135 *m/z* 118

2.1. MS/MS analysis of the product.



2.2. Distance effect during the reaction between ethyl acetoacetate (1a) and phenyl hydrazine (2a).





Figure S3. Distance effect during the reaction between ethyl acetoacetate and phenyl hydrazine showing greater conversion of the reactants to the final product at a distance of 5 cm.

2.3. Mass spectra for reaction between ethyl acetoacetate (1a) and phenyl hydrazine (2a) in EtOH.



Figure S4. Mass spectra for the reaction between ethyl acetoacetate and phenyl hydrazine in EtOH a) at 3 mm distance, b) at 4 cm distance with increasing distance, the Schiff base product is found to be most abundant in the mass spectra.

2.4. ¹H NMR spectrum of the Pyrazole product



Figure S5. ¹H NMR spectrum (300 MHz, CDCl₃) for the sprayed sample. The Schiff base product is also observed in the NMR experiment. No efforts were made to separate the mixture using chromatographic techniques. From the integration value the pyrazole product was found to be 50% of the Schiff base product.

3. Reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a).

3.1. Mass spectra of the reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a) in H₂O microdroplets.



Figure S6. Mass spectra of the reaction between heptane 3, 5-dione and phenyl hydrazine in water microdroplets a) at 3 mm and b) at 5 mm distance. The reaction shows greater conversion to product upon increasing distance of the sprayer from the inlet of the mass spectrometer.

3.2. Mass spectra of the reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a) in EtOH microdroplets.



Figure S7. Mass spectra of the reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a) in ethanol microdroplets (a) at 3 mm and b) 5 cm distance. The reaction shows greater conversion to product upon increasing distance of the sprayer from the inlet of the mass spectrometer.

3.3. MS/MS Characterization.



Figure S8. MS/MS spectrum for the product peak at m/z 201 and rationalized structures.

3.4. Proposed reaction mechanism and the intermediates in the mass spectrum.



Figure S9. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a).

3.5. ¹H NMR spectrum of the pyrazole product.



Figure S10. ¹H NMR (300 MHz, CDCl₃) of the pyrazole product formed in the reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a) in microdroplets.

4. Reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a).

4.1. Mass spectrum of the reaction in ethanol/water (80:20 v/v) microdroplets and MS/MS analysis of the resulting product.



Figure S11. (a) Reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a) in ethanol/water (80:20 v/v) microdroplets monitored online using a mass spectrometer. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS characterization of the pyrazole product showing cross ring fragmentation as the most abundant peak in the mass spectrum. The corresponding MS/MS fragmentations are rationalized in the figure.

4.2. Effect of using water during the reaction



Figure S12. Reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a) in (a) ethanol and (b) ethanol/water (80:20 v/v) mixture monitored online using a mass spectrometer.

4.3. Proposed reaction mechanism and the intermediates in the mass spectrum.



Figure S13. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a).

4.4. ¹H NMR spectrum of the pyrazole product.



Figure S14. ¹H NMR(300 MHz, CDCl₃) of the pyrazole product after reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a).

5. Reaction between ethyl acetoacetate (1a) and hydrazine hydrate (2b).

Although mass spectrum during this reaction showed only 2% conversion, the reagents were sprayed and collected for NMR analysis. From the ¹H NMR it has been found that there are no starting reagents present in the final product. The reduced conversion ratio (from the mass spectrum) might be due to

- 1. Low ionization efficiency of the pyrazole product as compared to other reaction intermediates.
- 2. The reaction might be a combination of microdroplet and thin film reaction.



5.1. Mass spectrum & MS/MS of reaction products in water microdroplets.

Figure S15. (a) Reaction between ethyl acetoacetate (1a) and hydrazine hydrate (2b) in water microdroplets monitored online using a mass spectrometer. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS characterization of the pyrazole product. The corresponding MS/MS fragmentations are rationalized in the figure.

5.2. Proposed reaction mechanism and the intermediates in the mass spectrum.



Figure S16. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between ethyl acetoacetate (1a) and hydrazine hydrate (2b).



Figure S17. (a) ¹H NMR (300 MHz, D_2O) for the mixture of ethyl acetoacetate (1a) and hydrazine hydrate (2b) showing peaks for the starting reagents. (b) ¹H NMR (300 MHz, DMSO-d₆) of the product formed as the result of the reaction between ethyl acetoacetate (1a) and hydrazine hydrate (2b) in microdroplets.

6. Reaction between heptane 3,5-dione (1b) and hydrazine hydrate (2b).



6.1. Mass spectrum & MS/MS of reaction products in water microdroplets

Figure S18. (a) Reaction between heptane 3,5-dione (1b) and hydrazine hydrate (2b) in water microdroplets monitored online using a mass spectrometer. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS spectrum for the product peak at m/z 125. The corresponding MS/MS fragmentations are rationalized in the figure.

6.2. Proposed reaction mechanism and the intermediates in the mass spectrum.



Figure S19. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between heptane 3,5-dione (1b) and hydrazine hydrate (2b) in water microdroplets.



Figure S20. ¹H NMR (300 MHz, D_2O) of the product for the reaction between heptane 3,5-dione (1b) and hydrazine hydrate (2b) in water microdroplets.

7. Reaction between 2-acetylcyclohexanone (1c) and hydrazine hydrate (2b).

7.1. Mass spectrum & MS/MS of reaction products in water microdroplets.



Figure S21. (a) Mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and hydrazine hydrate (2b) in water microdroplets. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS spectrum for the product peak at m/z 137. The corresponding MS/MS fragmentations are rationalized in the figure.

7.2. Proposed reaction mechanism and the intermediates in the mass spectrum.



Figure S22. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and hydrazine hydrate (2b) in water microdroplets.

7.3. ¹H NMR characterization of the pyrazole product.



Figure S23. ¹H NMR (300 MHz, D_2O) of the product for the reaction between 2-acetylcyclohexanone (1c) and hydrazine hydrate (2b) in water microdroplets.

8. Reaction between 1,3-diphenyl-1,3-propanedione (1d) and hydrazine hydrate (2b).

8.1. Mass spectrum & MS/MS of reaction products in water microdroplet.



Figure S24. (a) Mass spectrum of the reaction between 1,3-diphenyl-1,3-propanedione (1d) and hydrazine hydrate (2b) in ethanol. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS spectrum for the product peak at m/z 137. The corresponding MS/MS fragmentations are rationalized in the figure.

8.2. Proposed reaction mechanism and the intermediates in the mass spectrum.



Figure S25. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between 1,3-diphenyl-1,3-propanedione (1d) and hydrazine hydrate (2b) in ethanol microdroplets.

8.3. ¹H NMR characterization of the product.



Figure S26. ¹H NMR (300 MHz, CDCl₃) of the product for the reaction between 1,3-diphenyl-1,3-propanedione (1d) and hydrazine hydrate (2b) in ethanol microdroplets.

9. Reaction between 2-acetylcyclohexanone (1c) and 2-chloro-6-hydrazineylpyridine (2c).

9.1. Mass spectrum & MS/MS of reaction products in EtOH/Water (50:50) microdroplets.



Figure S27. (a) Mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and 2-chloro-6-hydrazineylpyridine (2c) in ethanol/water microdroplets. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS spectrum of product peak at m/z 248. The corresponding MS/MS fragmentations are rationalized in the figure.

9.2. Proposed reaction mechanism and the intermediates in the mass spectrum.



Figure S28. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and 2-chloro-6-hydrazineylpyridine (2c) in ethanol/water microdroplets.

10. Ecoscale Data:

Reference: Org. Lett. **2014**, 16 (19), 5060–5063 (Ecoscale value = 47.5)

Ecoscale calculate	pr										
-	2										
Reagents 🗵											
Link ide	ntifier*	name	MF*	MW	density	purity*	ml	a	mmoles	equiv.	
1 + -	Ethyl acetoacetate		C6H10O3	130.1436	1.03	100%	0.126353	0.130144	1	1	×
2 + -	Phenylhydrazine		C6H8N2	108.14292	1.09	100%	0.099214	0.108143	1	1	12 😣
3 + -	Acetic acid		C2H4O2	60.05256	1.048	100%	50	52.4	872.56896292	872.56896292	22 X
4 + -	Dichloromethane		CH2CI2	84.93288	1.325	100%	20	26.5	312.01108451	312.01108451	×
5 + -	Hydrochloric acid		HCI	36.46094		100%	0	0.036461][1	1	🕰 👌 桑 🗙 🗙
Products 🗵											
	identifier*: name:	s	MF*:	MW:	g:	mm	oles: g th	ieor: yiel	d:		
Conditions	1,2 00200		Contra								
Reagents	Name	mmoles eq.	Bp H	lazard P	rice						
	Ethyl acetoacetate	Infinity 1	180								
	Phenylhydrazine	Infinity 1	238	8							
	Dichloromethane	Infinity 312.01	39								
	Hydrochloric acid	Infinity 1	57 👌	.							
Yield	61				-19.5						
Price / availability					0						
Safety					-20						
Technical setup	Possible items Common set-up Instruments for controlled addit Unconventional activation tech	tion of chemicals	cted items nmon set-up ▲ ▼		0						
Temperature / time	Possible items reating, > 1h Heating, > 1h Cooling to 0°C	Sele Hei	<u>cted items</u> ating, > 1h ▲ ▼		-3						
Workup and purification	Possible items Sublimation Liquid - liquid extraction or was Classical chromatography	hing - Cla	cted items ssical chromatogra bling to room tempe ling solvent	phy rature	-10						
EcoScale					47.5						

Reference: *Synlett* **2018**, *29*, 2689–2692 (Ecoscale value = 51)

Ecoscale calculate	ог											
Reagents 🗵												
Link		name		*	MW	dansity		ml		mmoles	equity	
	Ethyl acetoacetate			C6H10O3	130 1436	1.03	100%	0.063177	0.065072	0.5	1	-
	Dhaaulhu	-desets -			100.1400	1.00	100%	0.000314	0.000012	1	[·	
	Phenyiny	rdrazine			100.14292	109	100%	0.099214	0.100145		2	
3 + -	Acetonitr	ile		CH3CN	41.05252	0.781	100%	2	1.562	38.048821363	76.097642726	👌 🖄 🗙 🗙
4 + -	Copper n	nitrate basic		Cu(NO3)2 . 3Cu	480.23784		100%	0	0.048024	0.1	0.2	
Products 🗵												
	identifier*: na	ame: 2-Diazole		MF*:	4N2 17	1: g: 5 0	mm	noles: g ti	heor: yie	ld:		
		,2-Diazoie				5 10			200333			
Conditions A												
Reagents	Ethyl acetoacetate	Infir	mmoles entry 1	q. Вр 180	Hazard	Price						
	Phenylhydrazine	Infir	nity 2	238	2							
	Acetonitrile	Infir	nity 76.09	81								
	Conner nitrate basis	Infr	,	0	(B)							
Vield	Copper Intrate basic		11Ly 0.2		۲							
Tielu Daias (ausilabilita	80]				-10		_				
Price / availability						-5						
Safety						-20						
Technical setup	Possible items Common set-up		Sele	nmon set-up								
	Instruments for control	olled addition of ch	emicals =	-	0	0						
Temperature / time	Possible items	auon tecninque	Sele	cted items								
	Room temperature, <	1h 🔺	Ro	om temperature, <	24h 🔺	-1						
	Room temperature, < Heating, < 1h	< 24h -			-	1						
Workup and purification	Possible items		Sele	cted items		_						
	Sublimation	ion or washing	Cla	ssical chromatogr	aphy with bn < 150°C	-13	-13					
	Classical chromatogr	aphy	Liq	uid - liquid extracti	ion or washing							
EcoScale						51						

Reference: Tetrahedron Letters **2008**, 49 (2), 397–400 (Ecoscale value = 48)

Ecoscale cal	culator												
Reage	ents 🗵												
🗹 Link	identifier	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.			
1 + -		3,5-Heptanedione	C7H12O2	128.17108	0.945	100%	0.135631	0.128171	1	1	×		
2 + -		Phenylhydrazine	C6H8N2	108.14292	1.09	100%	0.109135	0.118957	1.1	1.1	¥2 😣		
3 + -		Water	H2O	18.01528	1	100%	5	5	277.54217530	277.54217530			
4 -		Sulfonic acids, C6-12 alkane and C6-12 alka	r)			100%	0	0	0.1	0.1			
5 + -		Ethyl acetate	C4H8O2	88.10632	0.902	100%	20	18.04	204.75262160	204.75262160	8 🗙		
6 + -		Sodium bicarbonate	CHNaO3	84.00691		100%	0	5	59.518913384	59.518913384	te		
7 + -		n-Hexane	C6H14	86.17716	0.659	100%	5	3.295	38.235188999	38.235188999	8 1 × ×		
Produ	ucts 🗵												
	identif	er*: name:	MF	*: N	IW: g	: mr	moles: g	theor: yi	eld:				
		1,2-Diazole	Ca	BH4N2	200	0	0	.2 0					
Conditi	ons 🗵												
Rei	agents 3.5-He	Name			mmoles eq.	Bp Hazard Pri	ice						
	Phenyl	nydrazine			Infinity 1.1	238 1							
	Water				Infinity 277.54								
	Sulfoni	c acids, C6-12 alkane and C6-12 alkane hydroxy and	C6-12 alkene hyd	lroxy, sodium salts	Infinity 0.1		6						
	Ethyl a	cetate			Infinity 204.75	75							
	Sodium	bicarbonate			Infinity 59.51	y 59.51							
	n-Hexa	ne			Infinity 38.23	69 💧 🍢							
	Yield 92				-4								
Price / avai	lability				-5		_						
	Safety				-30								
Technical	setup Possible	items Sel	ected items										
	Instrur	on set-up Controlled addition of chemicals =	mmon set-up 🔺		0								
	Uncon	ventional activation technique	*										
Temperature	/ time Possible Room	tems Sel	ected items om temperature	. < 1h .									
	Room	temperature, < 24h =		-	0								
Workup and purif	ication Possible	items Sel	ected items										
Part - Part	None	Re	moval of solven	t with bp < 150°C	-13								
	Adding	solvent Cla	assical chromate	graphy	*								
Eco	Scale				48								

Reference: *Monatsh Chem* **2022**, *153* (3), 257–266 (Ecoscale value = 39)

Ecoscale calculat	or														
-															
Reagents 🗵															
Link											1008		100000000	100200	
id	entifier	diavasilana	name		MF		MW	der	sity	purity	mi	g	mmoles	equiv.	* *
		alpha H3Pt				12	2005 21220			100%		0.299	0.0009103104	1 2290 199753	0
3		Ethanol			C2H60		46.06904	0.79		100%	5	3.95	85 740879341	1054 8201323	
		Dhandhudanaina			CCHRND	0	100 14202	1.00		100%	0 100125	0.119057	1 4	12 522650726	
		Prierlyinydrazine			Conoinz		100.14292	1.09		100%	0.109135	0.110957		13.532659736	
5 +-		Ethyl acetoacetate			C6H10O3		130.1436	1.03		100%	0.126353	0.130144	1	12.30241/942	×
Products 🗵	i da esti Caratta					MC*				1000 C			2		
	Identifier":	1,2-Diazole	•			C3H4N	2 17	5	0	mm	oles: gt	014225 0	a:		
Conditions 🗵															
Reagents		Name	mmoles	eq.	Вр	Ha	azard	Price							
	dioxosilane		Infinity	204.75	75	٢									
	.alphaH3Pt		Infinity	1.22			6	0							
	Ethanol		Infinity	1054.82		8	<u>.</u>								
	Phenylhydra	zine	Infinity	13.53	238	¥2 §	<u>.</u>								
	Ethyl acetoa	cetate	Infinity	12.3	180										
Yield	80								-10						
Price / availability									-5		_				
Safety	a 11 1				1.1.1				-25						
rechnical setup	Any additio	nal special glasswa	re		conventional	activatio	on technique		-2						
	(Inert) gas a Glove box	atmosphere		- Co	mmon set-up	0		*	-2						
Temperature / time	Possible item	IS		Sele	cted items										
	Cooling to (°C =		Hei	ating, > 1n _ ating, > 1h	·			-6						
	Cooling, < (•C •				<u></u>									
Workup and purification	None None	IS	*	Rei	cted items moval of solv	ent with	bp < 150°C		12						
	Cooling to r Adding solv	oom temperature	-	Liq	uid - liquid e: ssical chrom	xtraction atograph	or washing hy		-13						
EcoScale						5 1			39					_	

Reference: This Work (Microdroplet Based Method)

For reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a) (Ecoscale value = 71)

Ecoscale calculate	or														
Reagents 🗵															
Link															
ide	entifier*		name	_	M	F [*]	MW	de D O O O	ensity	purity*	ml	g	mmoles	equiv.	
		3,5-Heptanedione			C/H120	12	128.17100	0.945	,	100%	13.563077	12.81/100			
2 + -		Phenylhydrazine			C6H8N2	1	108.14292	1.09		100%	9.921369	10.814292	100	1	1
3 + -		Water			H2O		18.01528	1		100%	5	5	277.54217530	2.7754217530	
Products 🗵	identifier*	: name: 1,2-Diazole	3			MF*: C3H4	IN2	MW: 200	g: 0		moles: g 1 0	theor: yi .649101 7	eld: 770.2961		
Reagents	3,5-Heptan Phenylhydr Water	Name Iedione razine	mmoles Infinity Infinity Infinity	eq. 1 1 2.77	Bp NaN 238	H	lazard	Price							
Yield	92								-4						
Price / availability									0						
Safety									-10						
Technical setup	Possible iter Any addition (Inert) gas Glove box	ns pnal special glasswai atmosphere	re ,	Selected Instrum Pressur Any ad	d items nents for controlled addition of chemicals re equipment, > 1 atm dditional special glassware			-5							
Temperature / time	Possible iter Room tem Room tem Heating, <	ns perature, < 1h iperature, < 24h : 1h	Roo	ected items oom temperature, < 1h			0								
Workup and purification	Possible iter Sublimatio Liquid - liq Classical (ns in juid extraction or was chromatography	ihing 🌲	Clas	cted items ssical chro	omatogra	aphy 🔺		-10						
EcoScale									71						

For reaction between ethyl acetoacetate (1a) and phenyl hydrazine (2a) (Ecoscale value = 52)

Ecoscale calculate	or										
Reagents 🗵											
Link					0.000		1112			21.22	
ide	entifier [*]	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.	
	Ethyl acetoacetate			130.1430	1.05	100%	12.035301	13.01436			~
	Water			10.01520		100%	1000		55506.435061	555.06435061	
3 + -	Phenylhydrazine		C6H8N2	108.1429	2 1.09	100%	9.921369	10.814292	100	1	
Products 🗵	identifier*: name:	9	۲ 	MF*: C3H4N2	MW: g: 175 0		noles: g t 17	heor: yie 7.5 0	ld:		
Conditions 🗵											
Reagents	Name Ethyl acetoacetate Water Phenylhydrazine	mmoles Infinity 1 Infinity 555. Infinity 1	eq. Bp 180 08 238	Hazard	Price						
Yield	52				-24						
Price / availability					0						
Safety					-10						
Technical setup	Possible items Common set-up Instruments for controlled addi Unconventional activation tech	tion of chemicals	cted items truments for cont ssure equipment	rolled addition of t, > 1 atm	chemicals						
Temperature / time	Possible items Room temperature, < 1h Room temperature, < 24h Heating, < 1h		Selected items Room temperati	ure, < 1h ▲ ▼	0						
Workup and purification	Possible items Sublimation Liquid - liquid extraction or was Classical chromatography	shing	Selected items Classical chrom	atography 🔺	-10						
EcoScale					52						