Supporting Information

Accelerated Synthesis of Pyrazoles Mediated by Water Microdroplets

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

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1. Additional Experimental Details

1.1. Collection Setup for Scale Up Experiment:

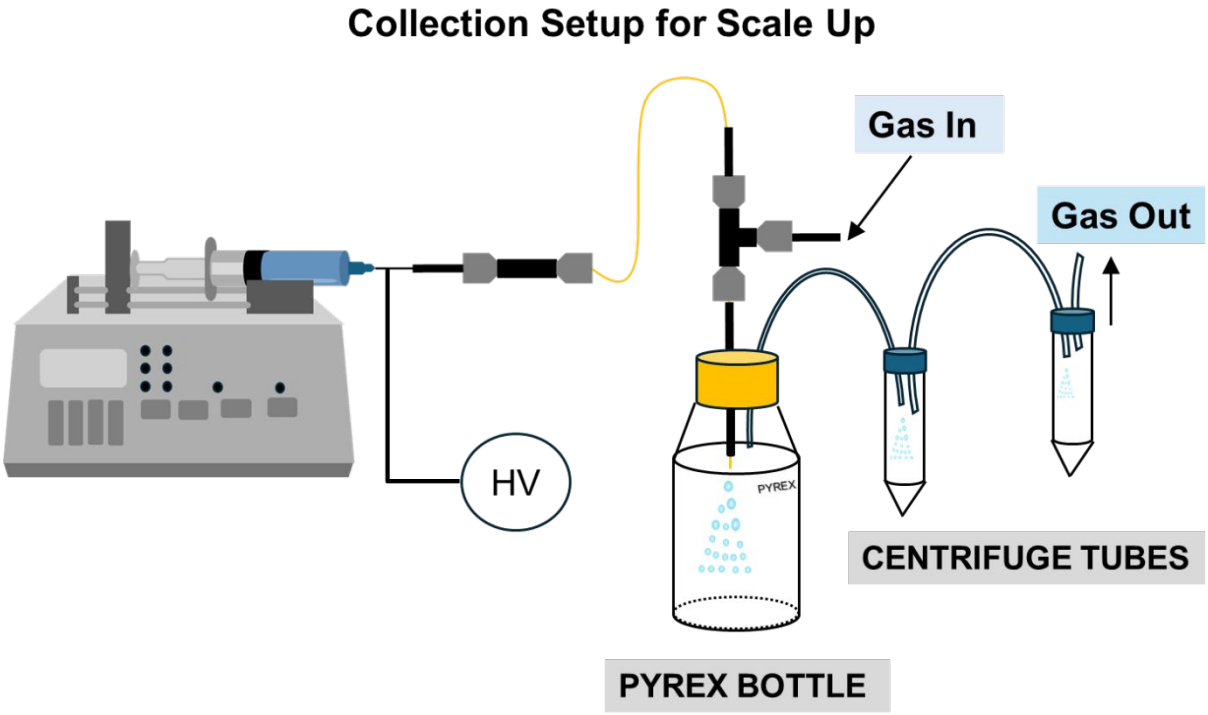

Figure S1. Schematic representation of the collection setup for scale up experiments.

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:

$$\text{Conversion Ratio} = \frac{I_P}{I_P + I_R + I_{INT}} * 100\ \% \quad \text{---------- (1)}$$

$$\text{Conversion Ratio} = \frac{I_P}{I_P + I_R} * 100\ \% \quad \text{---------- (2)}$$

$$\text{Conversion Ratio} = \frac{I_P + I_{INT}}{I_P + I_R + I_{INT}} * 100\ \% \quad \text{---------- (3)}$$

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).

2.1. MS/MS analysis of the product.

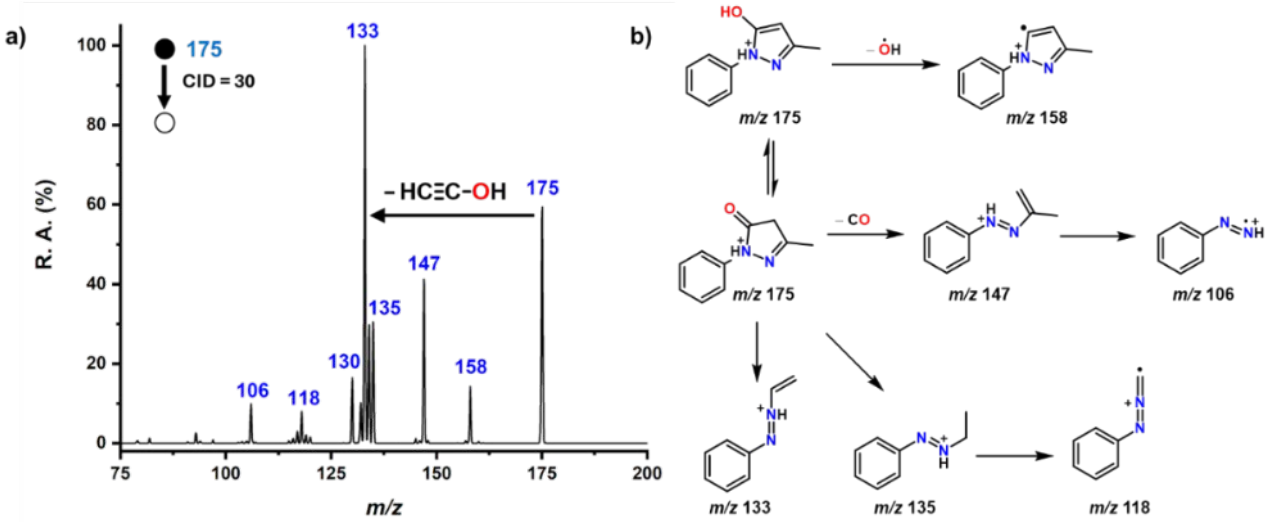

Figure S2. (a) MS/MS spectrum of product peak at *m/z* 175, (b) ChemDraw depiction of the rationalized MS/MS fragmentations.

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

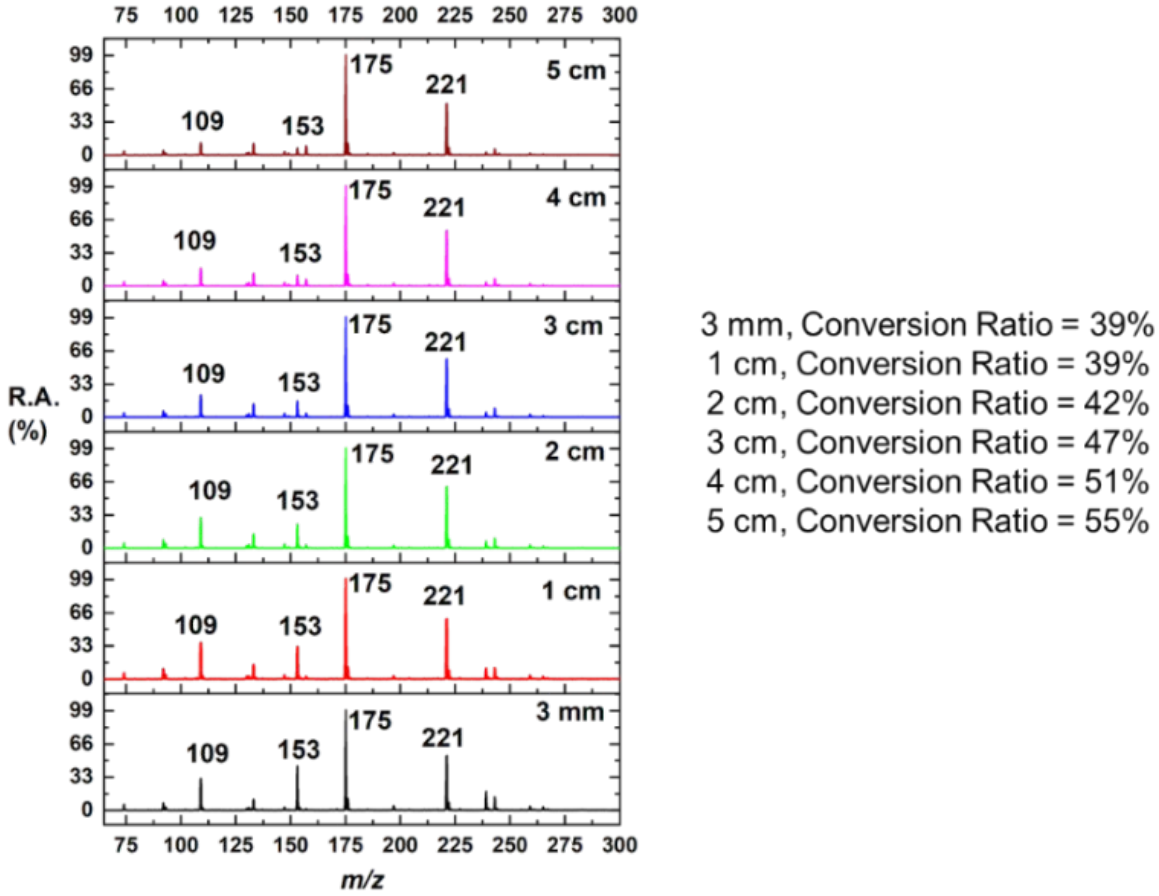

Figure S3. Distance effect during the reaction between ethyl acetoacetate and phenyl hydrazine showing greater conversion of the reactants to the final product at a distance of 5 cm.

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

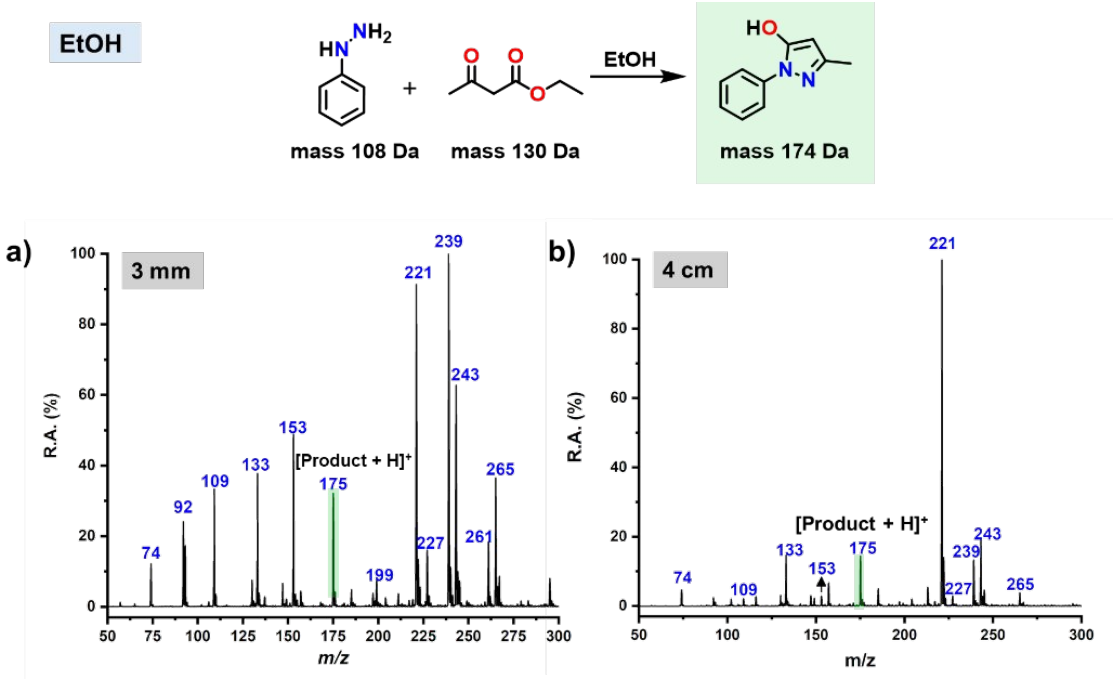

Figure S4. Mass spectra for the reaction between ethyl acetoacetate and phenyl hydrazine in EtOH a) at 3 mm distance, b) at 4 cm distance with increasing distance, the Schiff base product is found to be most abundant in the mass spectra.

2.4. ^{1}H NMR spectrum of the Pyrazole product

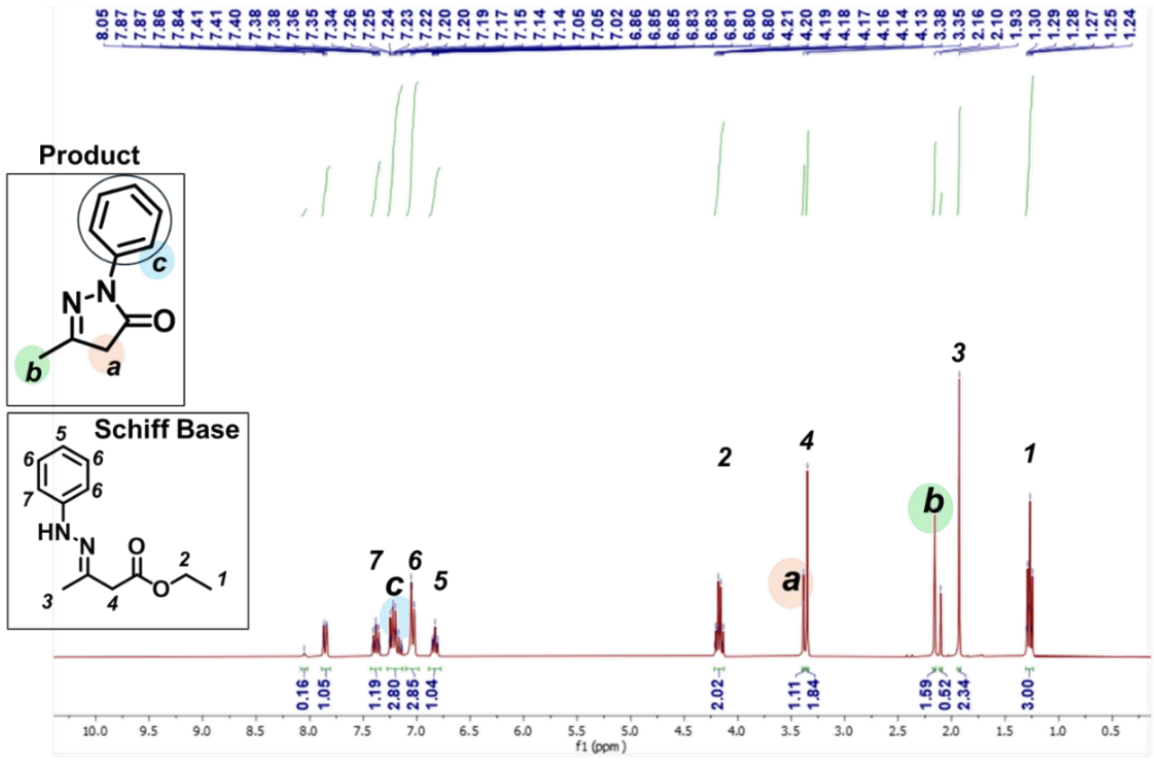

Figure S5. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) for the sprayed sample. The Schiff base product is also observed in the NMR experiment. No efforts were made to separate the mixture using chromatographic techniques. From the integration value the pyrazole product was found to be 50% of the Schiff base 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 H_2O microdroplets.

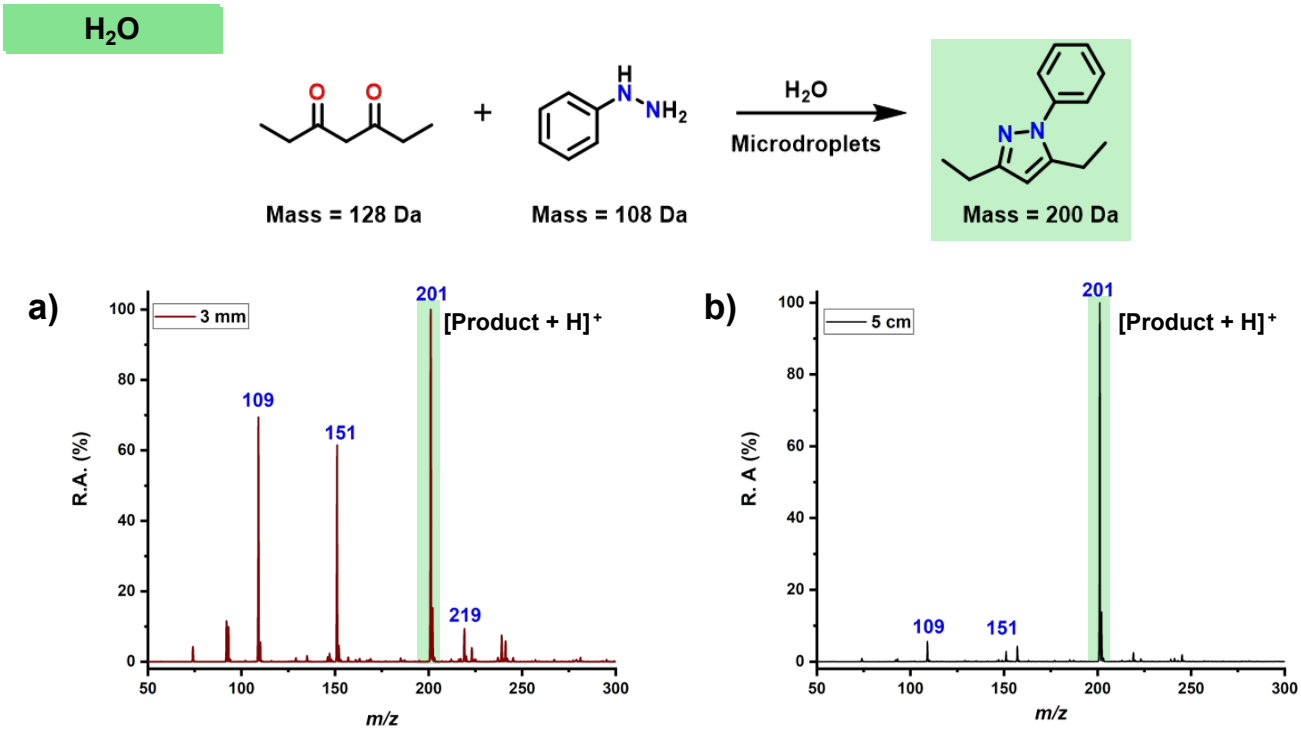

Figure S6. Mass spectra of the reaction between heptane 3, 5-dione and phenyl hydrazine in water microdroplets a) at 3 mm and b) at 5 mm distance. The reaction shows greater conversion to product upon increasing distance of the sprayer from the inlet of the mass spectrometer.

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

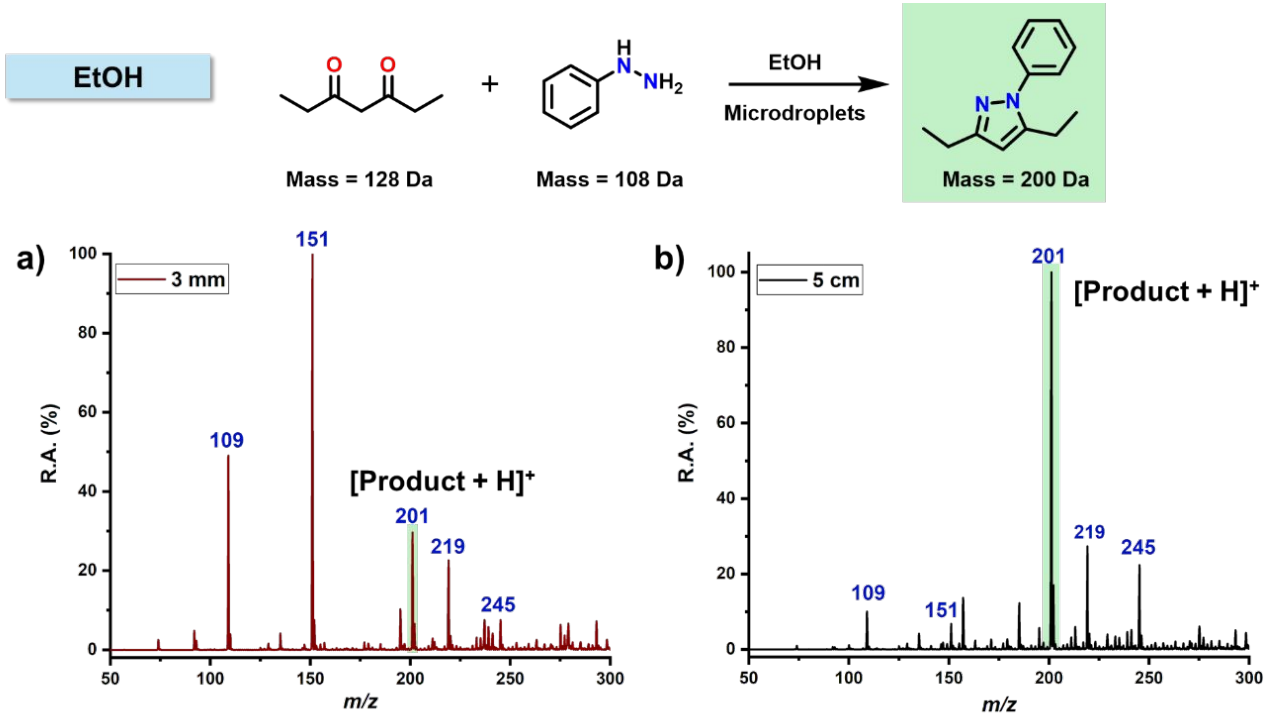

Figure S7. Mass spectra of the reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a) in ethanol microdroplets (a) at 3 mm and b) 5 cm distance. The reaction shows greater conversion to product upon increasing distance of the sprayer from the inlet of the mass spectrometer.

3.3. MS/MS Characterization.

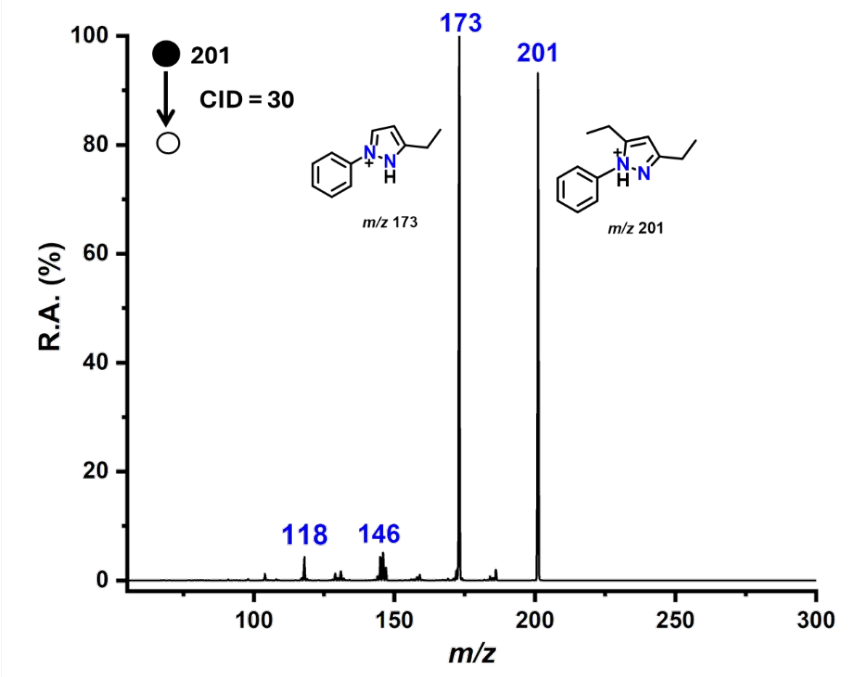

Figure S8. MS/MS spectrum for the product peak at *m/z* 201 and rationalized structures.

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

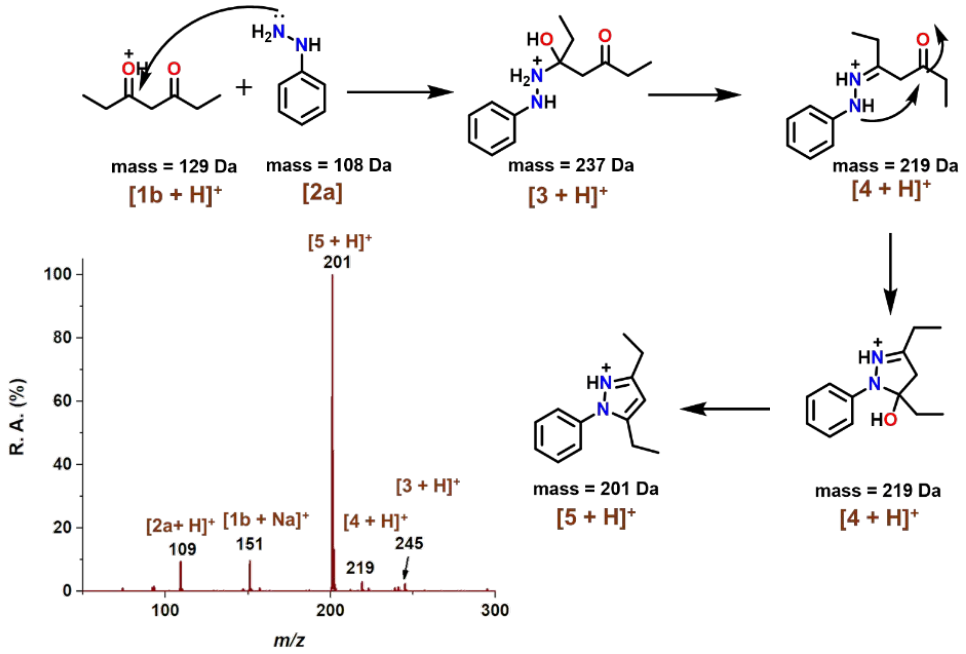

Figure S9. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a).

3.5. ^{1}H NMR spectrum of the pyrazole product.

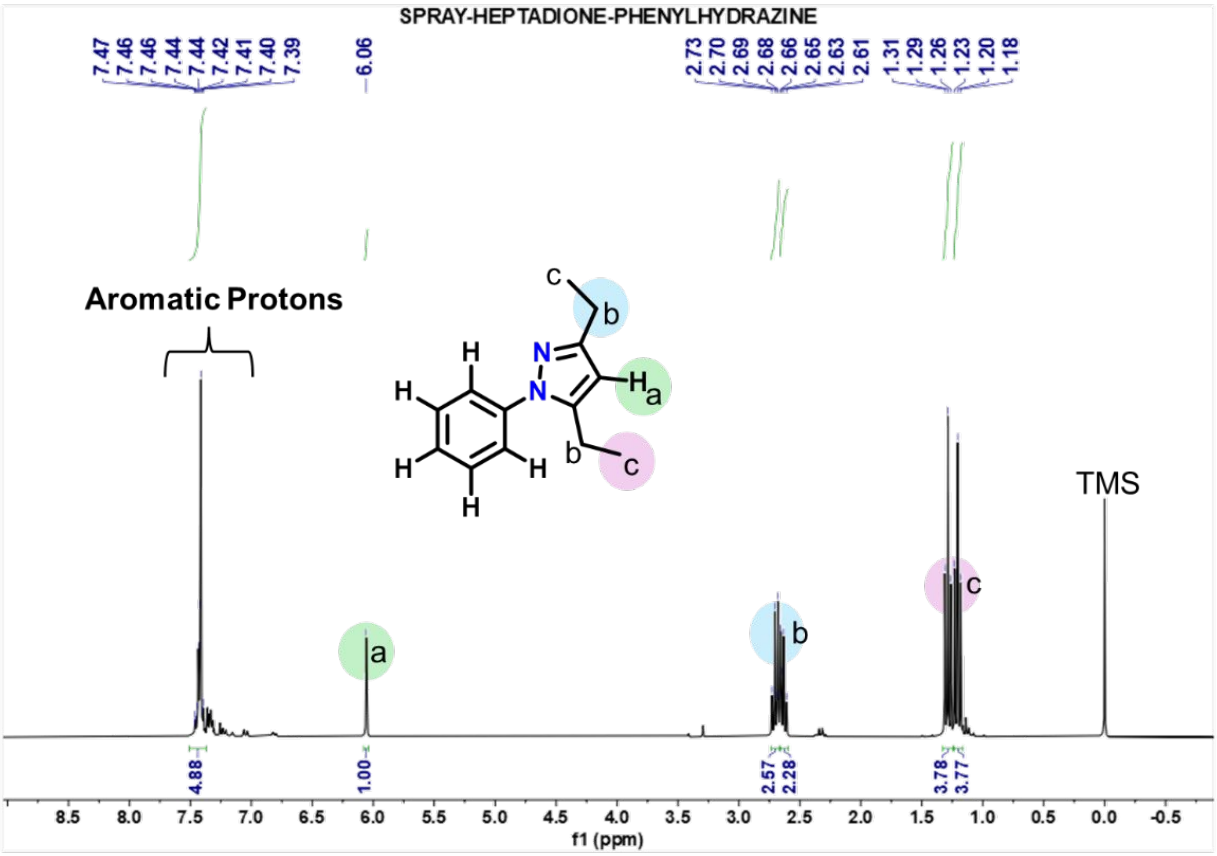

Figure S10. ^{1}H NMR (300 MHz, $CDCl_3$) of the pyrazole product formed in the reaction between heptane 3,5-dione (1b) and phenyl hydrazine (2a) in microdroplets.

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.

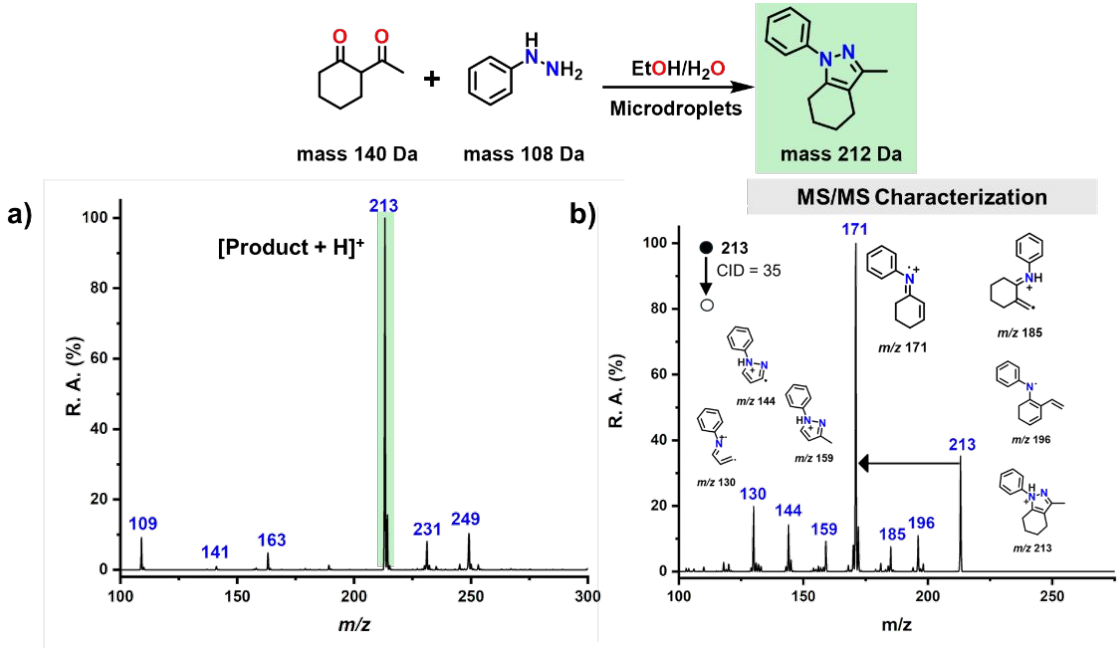

Figure S11. (a) Reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a) in ethanol/water (80:20 v/v) microdroplets monitored online using a mass spectrometer. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS characterization of the pyrazole 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

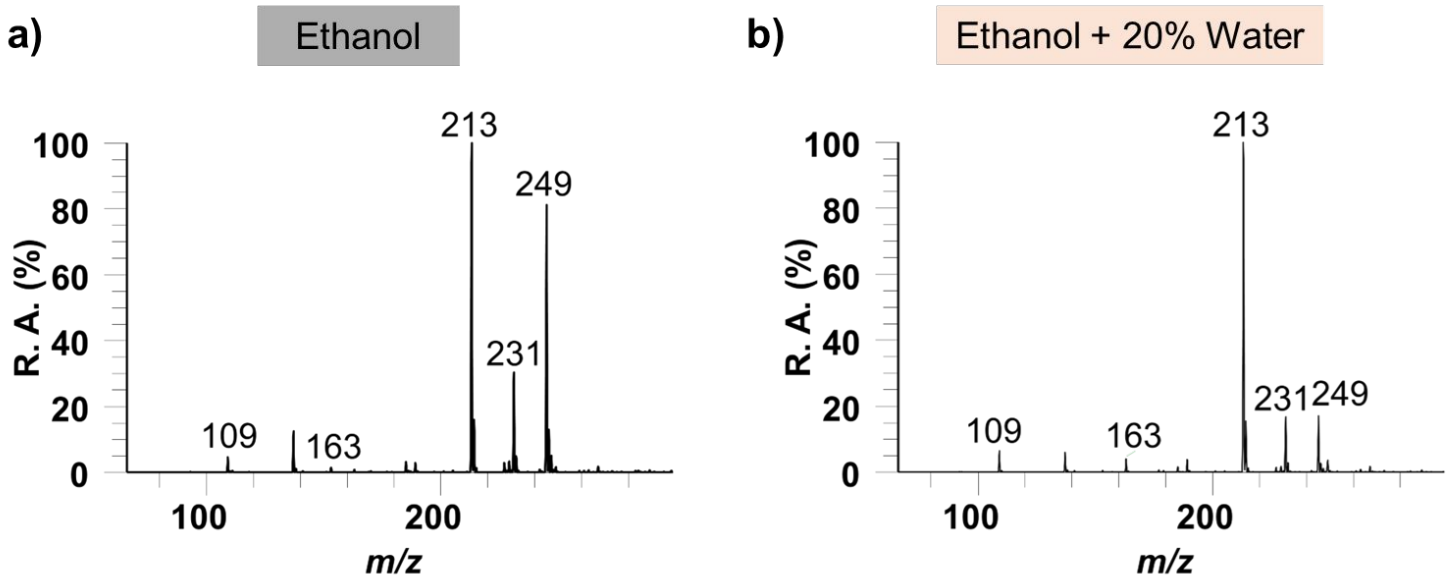

Figure S12. Reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a) in (a) ethanol and (b) ethanol/water (80:20 v/v) mixture monitored online using a mass spectrometer.

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

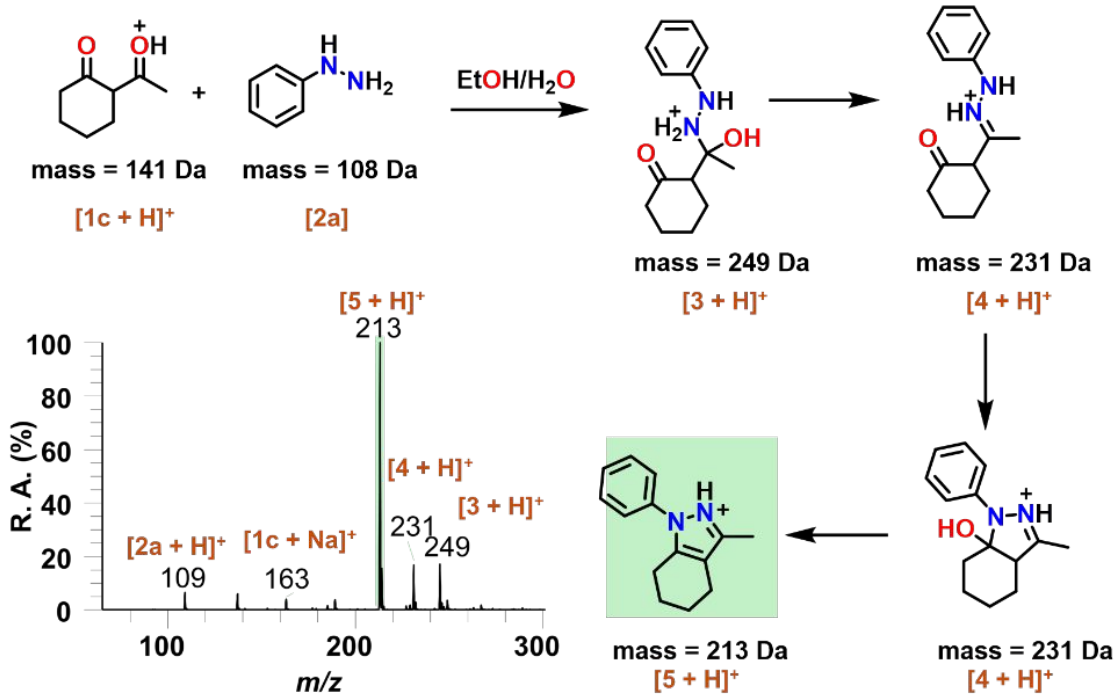

Figure S13. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a).

4.4. ^{1}H NMR spectrum of the pyrazole product.

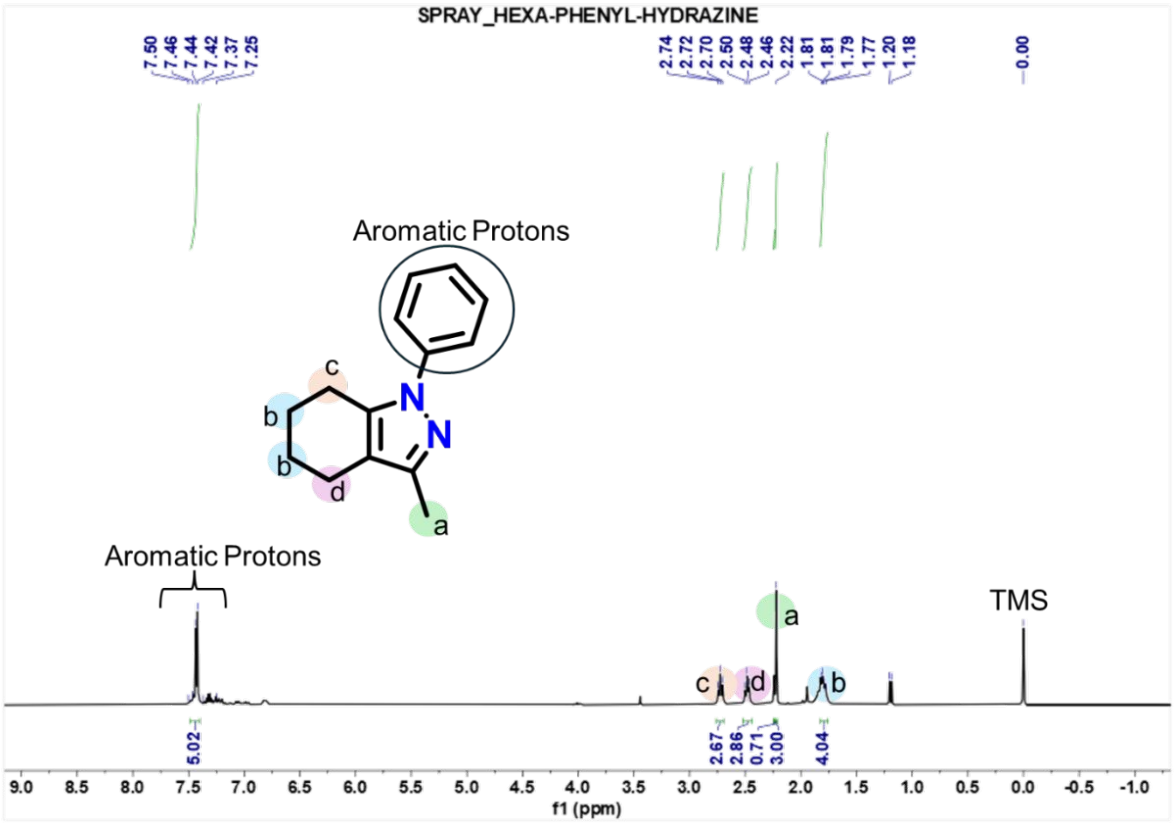

Figure S14. ^{1}H NMR(300 MHz, $CDCl_3$) of the pyrazole product after reaction between 2-acetylcyclohexanone (1c) and phenyl hydrazine (2a).

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 ^{1}H 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.

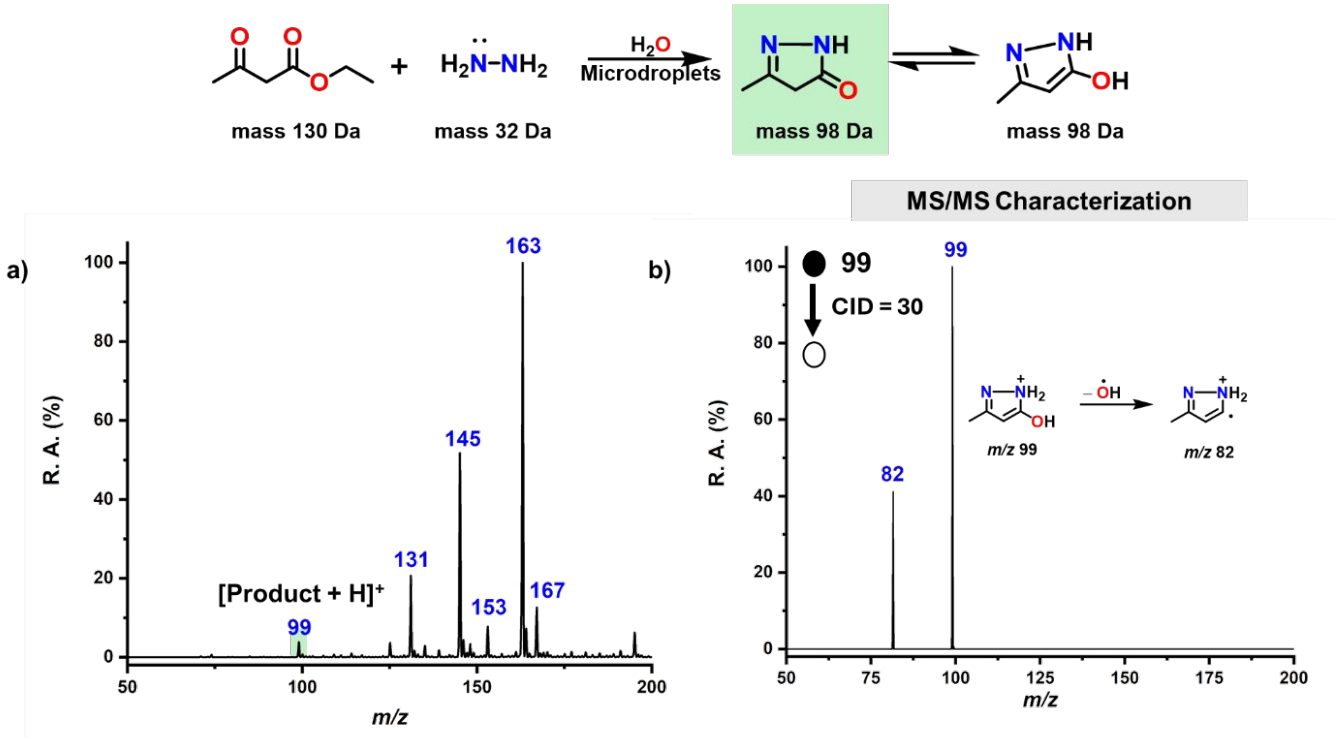

Figure S15. (a) Reaction between ethyl acetoacetate (1a) and hydrazine hydrate (2b) in water microdroplets monitored online using a mass spectrometer. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS characterization of the pyrazole product. The corresponding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

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

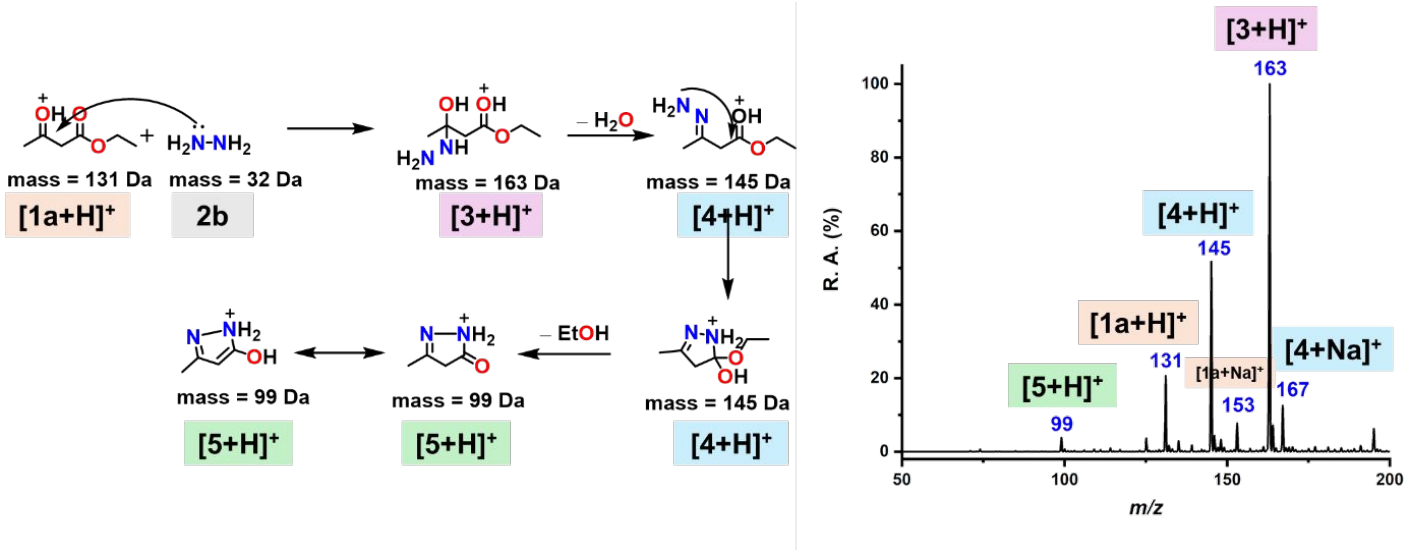

Figure S16. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between ethyl acetoacetate (1a) and hydrazine hydrate (2b).

5.3. ^{1}H NMR characterization.

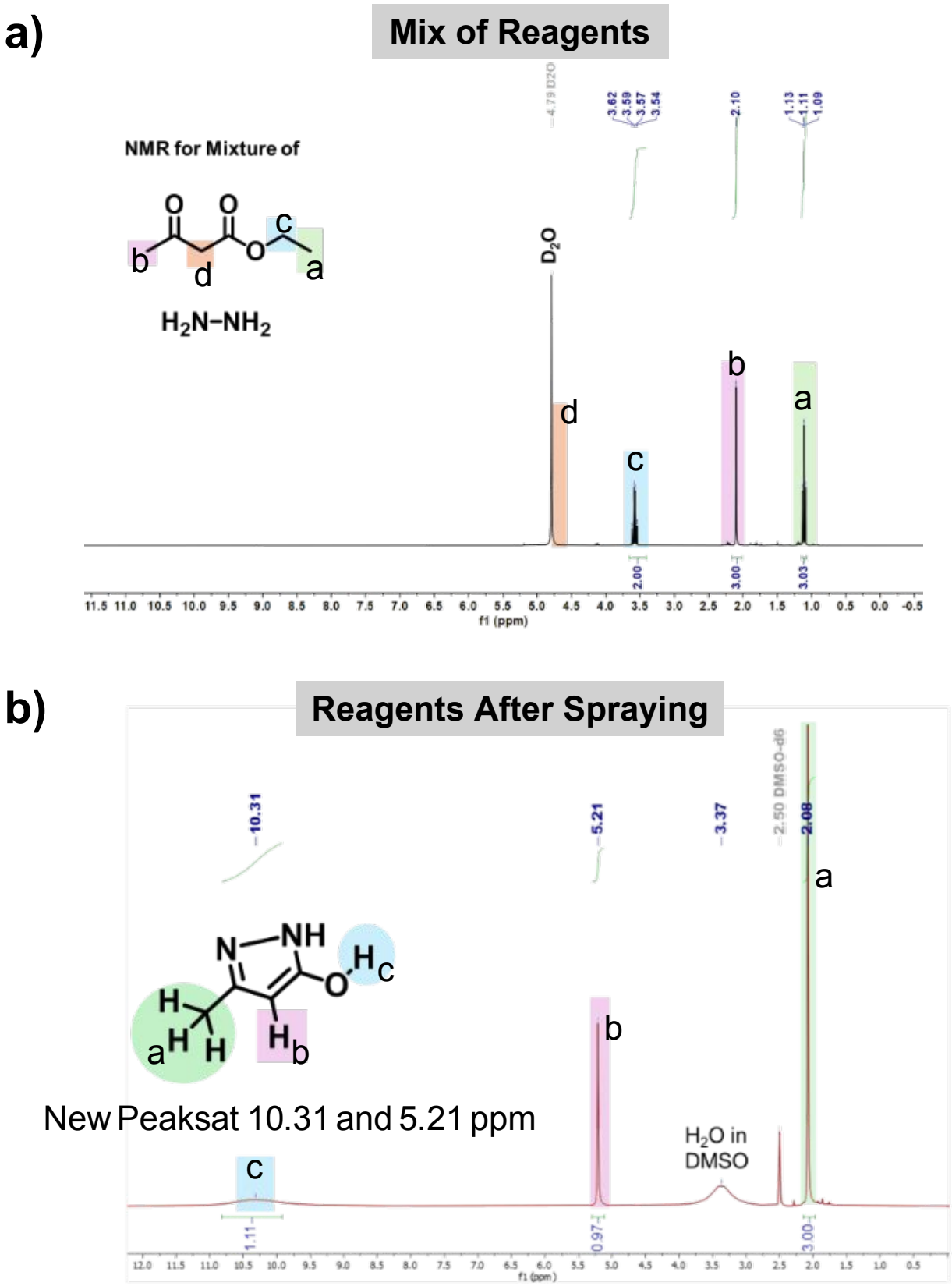

Figure S17. (a) ^{1}H NMR (300 MHz, D_2O) for the mixture of ethyl acetoacetate (1a) and hydrazine hydrate (2b) showing peaks for the starting reagents. (b) ^{1}H NMR (300 MHz, DMSO-d_6) of the product formed as the result of the reaction between ethyl acetoacetate (1a) and hydrazine hydrate (2b) in 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

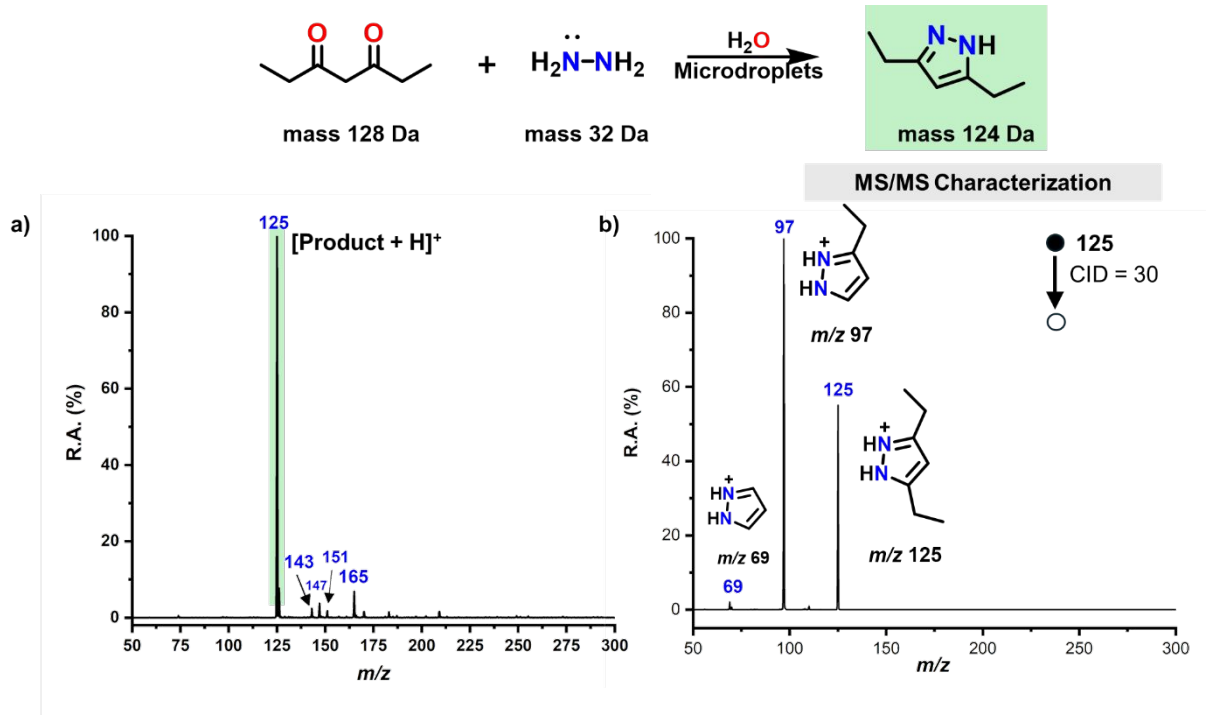

Figure S18. (a) Reaction between heptane 3,5-dione (1b) and hydrazine hydrate (2b) in water microdroplets monitored online using a mass spectrometer. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS spectrum for the product peak at *m/z* 125. The corresponding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

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

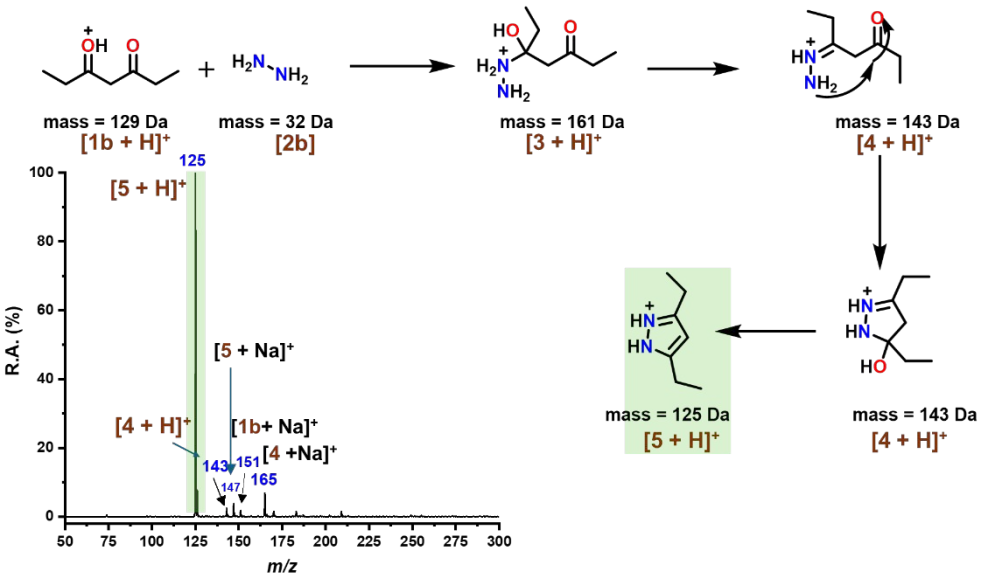

Figure S19. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between heptane 3,5-dione (1b) and hydrazine hydrate (2b) in water microdroplets.

6.3. ^{1}H NMR characterization of the product

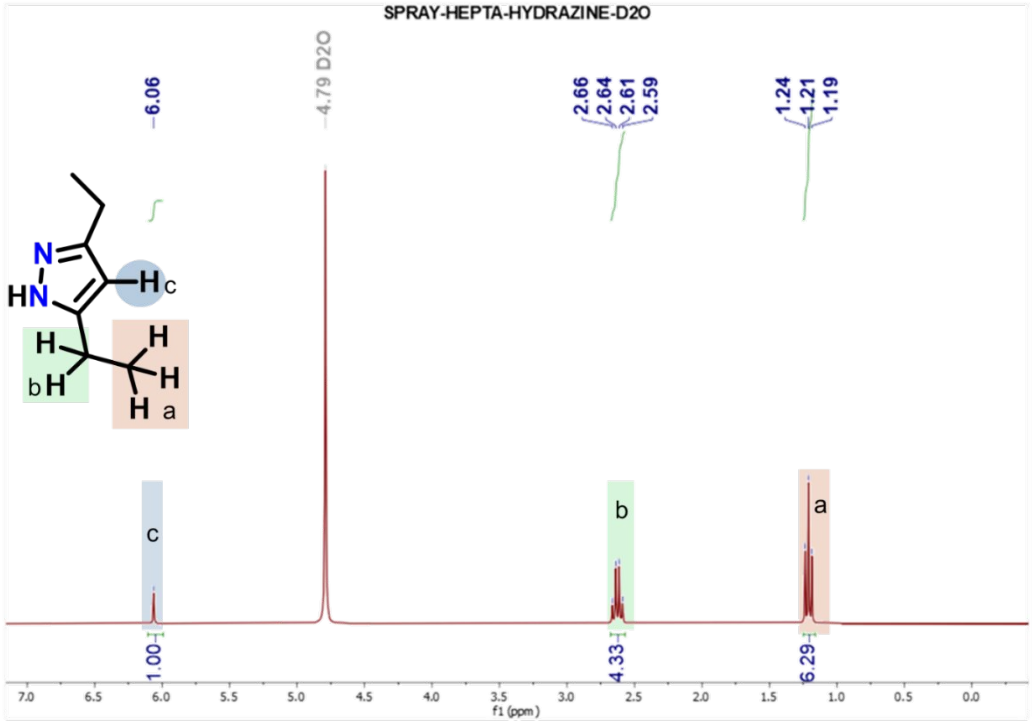

Figure S20. ^{1}H NMR (300 MHz, D_2O) of the product for the reaction between heptane 3,5-dione (1b) and hydrazine hydrate (2b) in water microdroplets.

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

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

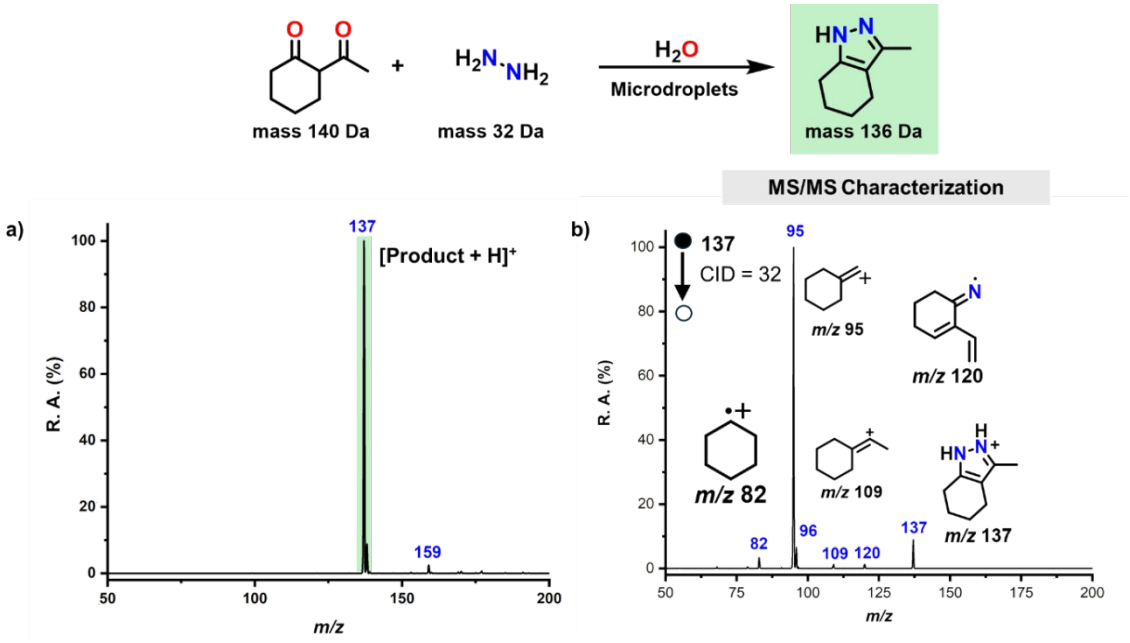

Figure S21. (a) Mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and hydrazine hydrate (2b) in water microdroplets. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS spectrum for the product peak at *m/z* 137. The corresponding MS/MS fragmentations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

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

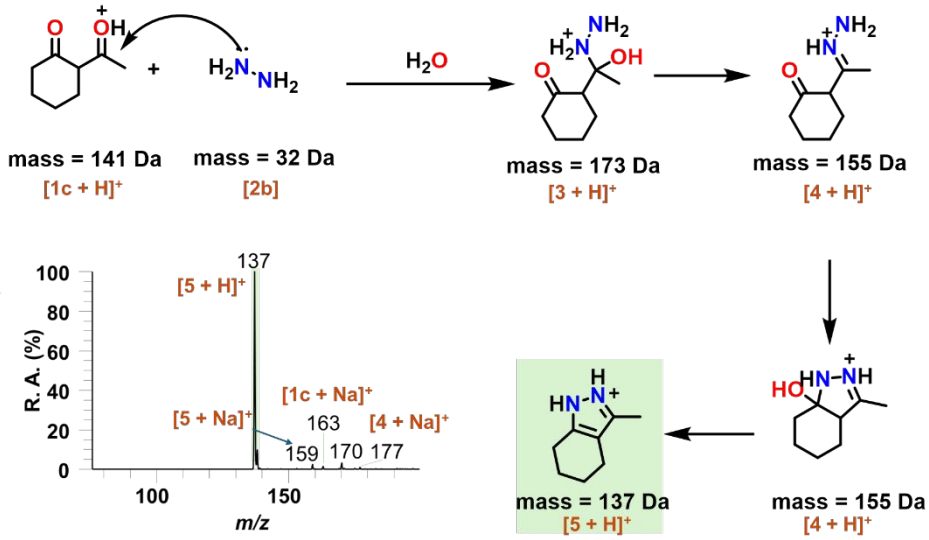

Figure S22. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and hydrazine hydrate (2b) in water microdroplets.

7.3. ^{1}H NMR characterization of the pyrazole product.

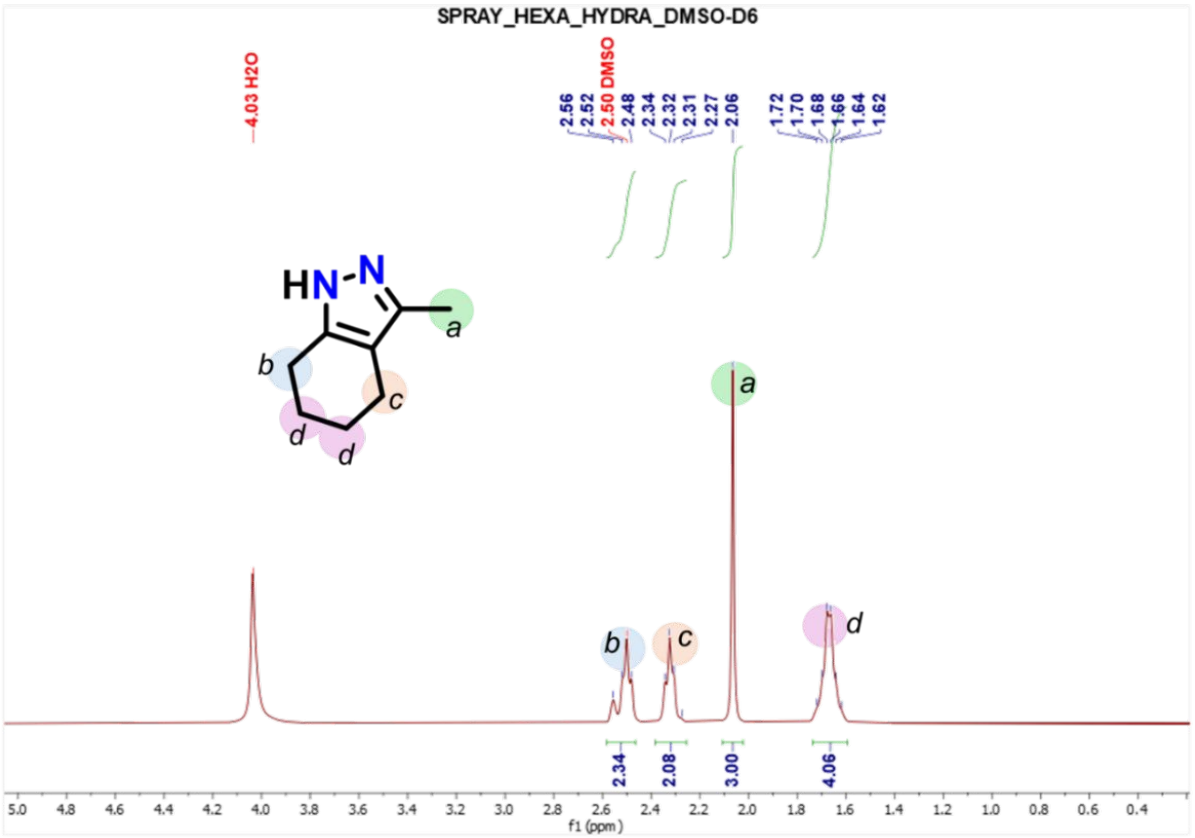

Figure S23. ^{1}H NMR (300 MHz, D_2O) of the product for the reaction between 2-acetylcyclohexanone (1c) and hydrazine hydrate (2b) in water microdroplets.

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**.**

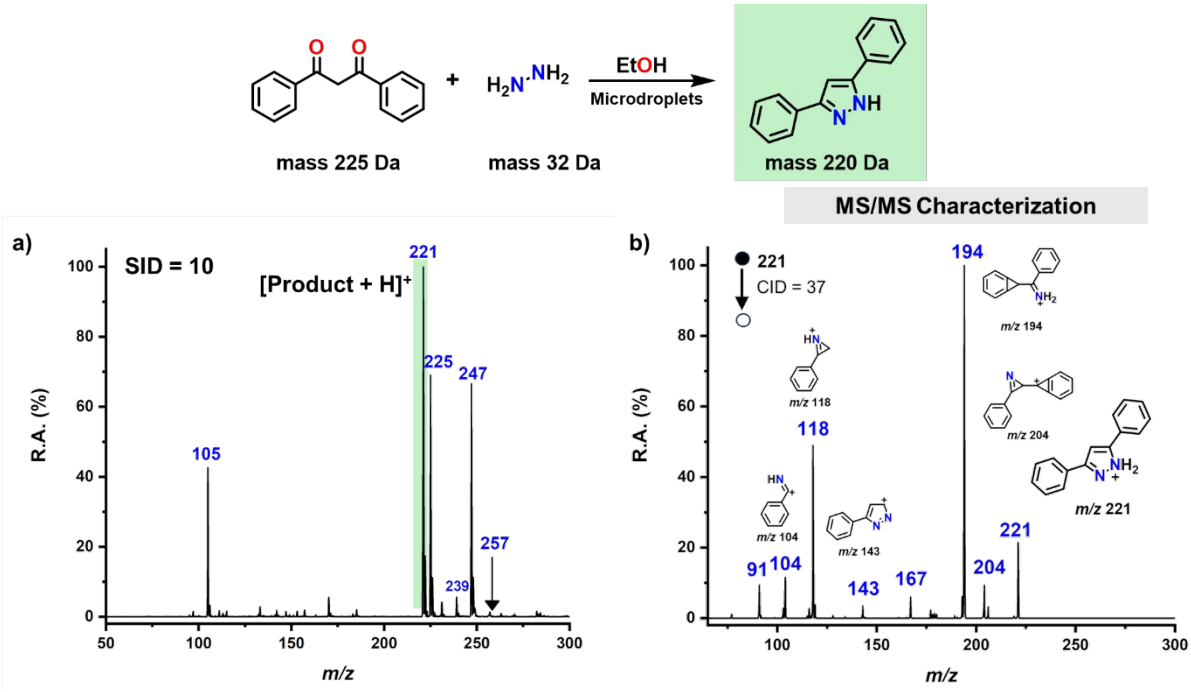

Figure S24. (a) Mass spectrum of the reaction between 1,3-diphenyl-1,3-propanedione (1d) and hydrazine hydrate (2b) in ethanol. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS spectrum for the product peak at *m/z* 137. The corresponding MS/MS fragmentations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

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

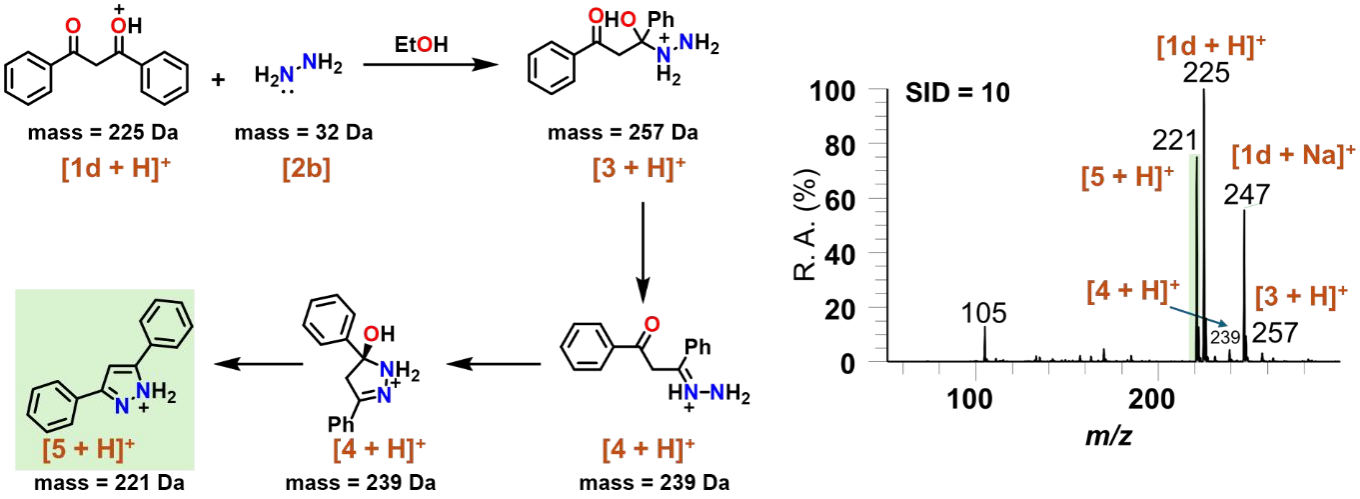

Figure S25. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between 1,3-diphenyl-1,3-propanedione (1d) and hydrazine hydrate (2b) in ethanol microdroplets.

8.3. ^{1}H NMR characterization of the product.

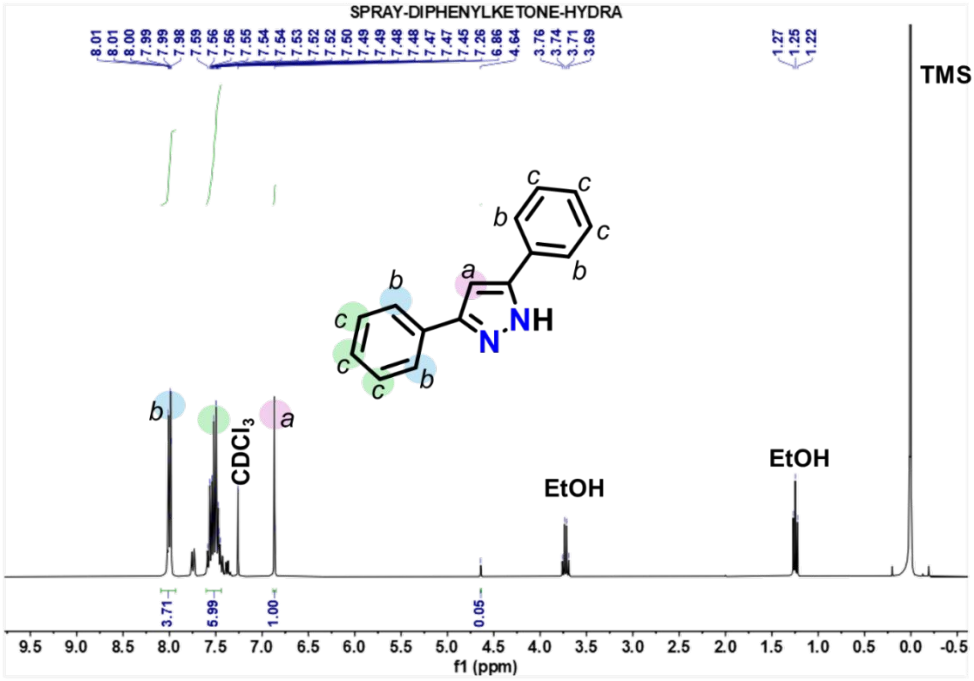

Figure S26. ^{1}H NMR (300 MHz, $CDCl_3$) of the product for the reaction between 1,3-diphenyl-1,3-propanedione (1d) and hydrazine hydrate (2b) in ethanol microdroplets.

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**.**

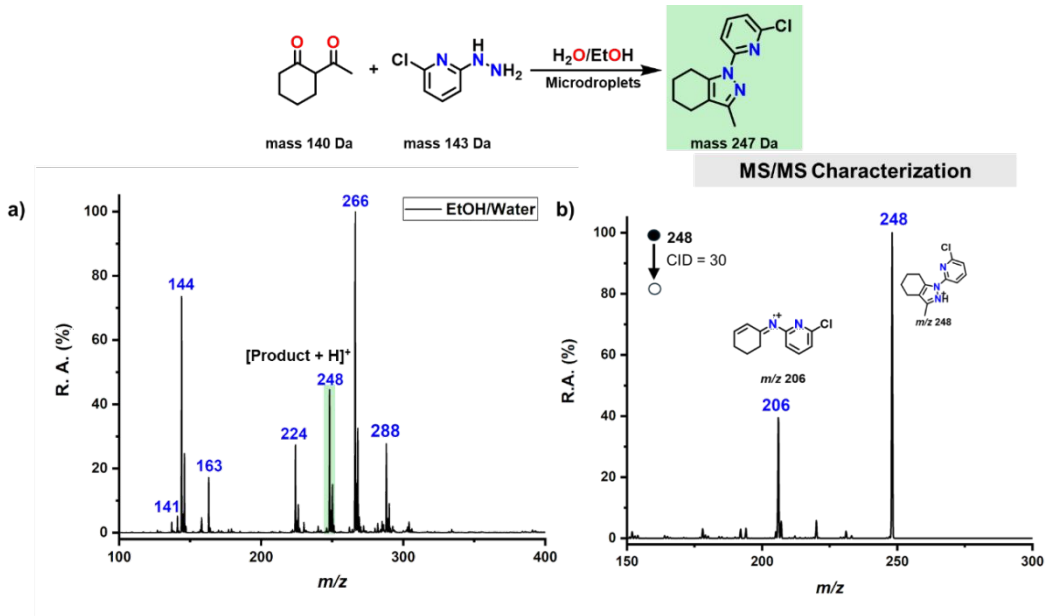

Figure S27. (a) Mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and 2-chloro-6-hydrazineylpyridine (2c) in ethanol/water microdroplets. The distance of the sprayer was kept 20 mm away from the inlet of the mass spectrometer. (b) MS/MS spectrum of product peak at *m/z* 248. The corresponding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

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

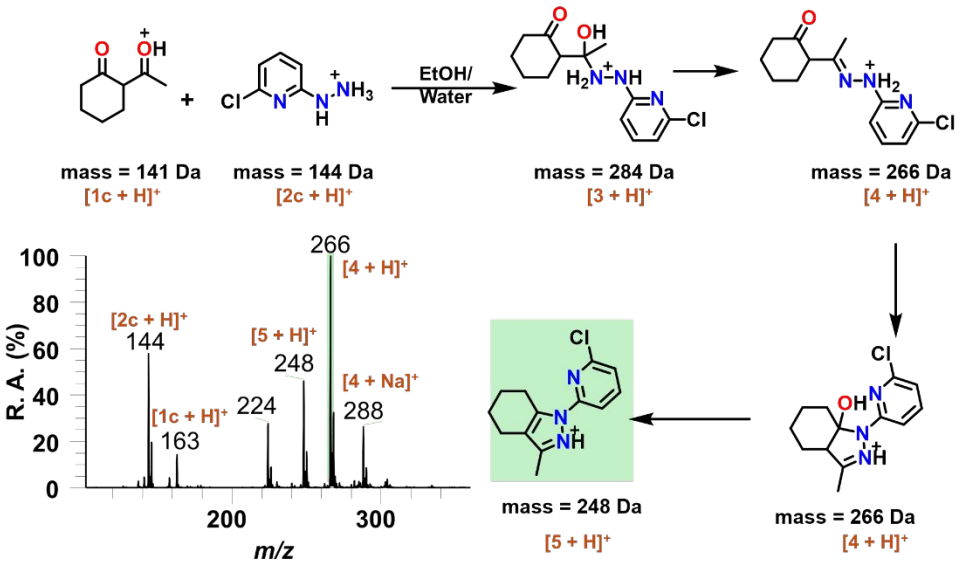

Figure S28. Proposed reaction mechanism and the intermediates and products as determined from the mass spectrum for the reaction between 2-acetylcyclohexanone (1c) and 2-chloro-6-hydrazineylpyridine (2c) in ethanol/water microdroplets.

10. Ecoscale Data:

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

Ecoscale calculator

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	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
3		Acetic acid	C2H4O2	60.05256	1.048	100%	50	52.4	872.56896292	872.56896292
4		Dichloromethane	CH2Cl2	84.93288	1.325	100%	20	26.5	312.01108451	312.01108451
5		Hydrochloric acid	HCl	36.46094		100%	0	0.036461	1	1

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	1,2-Diazole	C3H4N2	175	0		0.175	0

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Ethyl acetoacetate	Infinity	1	180		
Phenylhydrazine	Infinity	1	238		
Acetic acid	Infinity	872.56	117		
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 addition of chemicals; Unconventional activation technique — Selected items: Common set-up	0
Temperature / time	Possible items: Heating, > 1h; Cooling to 0°C — Selected items: Heating, > 1h	-3
Workup and purification	Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography — Selected items: Classical chromatography; Cooling to room temperature; Adding solvent	-10
EcoScale		47.5

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

Ecoscale calculator

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		Ethyl acetoacetate	C6H10O3	130.1436	1.03	100%	0.063177	0.065072	0.5	1
2		Phenylhydrazine	C6H8N2	108.14292	1.09	100%	0.099214	0.108143	1	2
3		Acetonitrile	CH3CN	41.05252	0.781	100%	2	1.562	38.048821363	76.097642726
4		Copper nitrate basic	Cu(NO3)2 . 3Cu(	480.23784		100%	0	0.048024	0.1	0.2

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	1,2-Diazole	C3H4N2	175	0		1.200595	4

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Ethyl acetoacetate	Infinity	1	180		
Phenylhydrazine	Infinity	2	238		
Acetonitrile	Infinity	76.09	81		
Copper nitrate basic	Infinity	0.2			

Yield	80	-10
Price / availability		-5
Safety		-20
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique — Selected items: Common set-up	0
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h — Selected items: Room temperature, < 24h	-1
Workup and purification	Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography — Selected items: Classical chromatography; Removal of solvent with bp < 150°C; Liquid - liquid extraction or washing	-13
EcoScale		51

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

Ecoscale calculator

Reagents

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
3		Water	H2O	18.01528	1	100%	5	5	277.54217530	277.54217530
4		Sulfonic acids, C6-12 alkane and C6-12 alkar				100%	0	0	0.1	0.1
5		Ethyl acetate	C4H8O2	88.10632	0.902	100%	20	18.04	204.75262160	204.75262160
6		Sodium bicarbonate	CHNaO3	84.00691		100%	0	5	59.518913384	59.518913384
7		n-Hexane	C6H14	86.17716	0.659	100%	5	3.295	38.235188999	38.235188999

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	1,2-Diazole	C3H4N2	200	0		0.2	0

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
3,5-Heptanedione	Infinity	1	NaN		
Phenylhydrazine	Infinity	1.1	238		
Water	Infinity	277.54			
Sulfonic acids, C6-12 alkane and C6-12 alkane hydroxy and C6-12 alkene hydroxy, sodium salts	Infinity	0.1			
Ethyl acetate	Infinity	204.75	75		
Sodium bicarbonate	Infinity	59.51			
n-Hexane	Infinity	38.23	69		

Yield	92	-4
Price / availability		-5
Safety		-30
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique — Selected items: Common set-up	0
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h — Selected items: Room temperature, < 1h	0
Workup and purification	Possible items: None; Cooling to room temperature; Adding solvent — Selected items: Removal of solvent with bp < 150°C; Liquid - liquid extraction or washing; Classical chromatography	-13
EcoScale		48

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

Ecoscale calculator

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		dioxosilane	O2Si	60.0843		100%	0	1	16.643282854	204.75262160
2		.alpha.-H3Pt	H8O40PW12	2885.21328		100%	0	0.288	0.0998193104	1.2280188753
3		Ethanol	C2H6O	46.06904	0.79	100%	5	3.95	85.740879341	1054.8201323
4		Phenylhydrazine	C6H8N2	108.14292	1.09	100%	0.109135	0.118957	1.1	13.532659736
5		Ethyl acetoacetate	C6H10O3	130.1436	1.03	100%	0.126353	0.130144	1	12.302417942

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	1,2-Diazole	C3H4N2	175	0		0.014225	0

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
dioxosilane	Infinity	204.75	75		
.alpha.-H3Pt	Infinity	1.22			
Ethanol	Infinity	1054.82			
Phenylhydrazine	Infinity	13.53	238		
Ethyl acetoacetate	Infinity	12.3	180		

Yield	80	-10
Price / availability		-5
Safety		-25
Technical setup	Possible items: Any additional special glassware; (Inert) gas atmosphere; Glove box. Selected items: Unconventional activation technique; Common set-up	-2
Temperature / time	Possible items: Heating, > 1h; Cooling to 0°C; Cooling, < 0°C. Selected items: Heating, > 1h; Heating, > 1h	-6
Workup and purification	Possible items: None; Cooling to room temperature; Adding solvent. Selected items: Removal of solvent with bp < 150°C; Liquid - liquid extraction or washing; Classical chromatography	-13
EcoScale		39

Reference: This Work (Microdroplet Based Method)

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

Ecoscale calculator

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		3,5-Heptanedione	C7H12O2	128.17108	0.945	100%	13.563077	12.817108	100	1
2		Phenylhydrazine	C6H8N2	108.14292	1.09	100%	9.921369	10.814292	100	1
3		Water	H2O	18.01528	1	100%	5	5	277.54217530	2.7754217530

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	1,2-Diazole	C3H4N2	200	0		0.649101	770.2961

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
3,5-Heptanedione	Infinity	1	NaN		
Phenylhydrazine	Infinity	1	238		
Water	Infinity	2.77			

Yield	92	-4
Price / availability		0
Safety		-10
Technical setup	Possible items: Any additional special glassware; (Inert) gas atmosphere; Glove box. Selected items: Instruments for controlled addition of chemicals; Pressure equipment, > 1 atm; Any additional special glassware	-5
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h. Selected items: Room temperature, < 1h	0
Workup and purification	Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography. Selected items: Classical chromatography	-10
EcoScale		71

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

Ecoscale calculator

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		Ethyl acetoacetate	C6H10O3	130.1436	1.03	100%	12.635301	13.01436	100	1
2		Water	H2O	18.01528	1	100%	1000	1000	55508.435061	555.08435061
3		Phenylhydrazine	C6H8N2	108.14292	1.09	100%	9.921369	10.814292	100	1

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	1,2-Diazole	C3H4N2	175	0		17.5	0

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Ethyl acetoacetate	Infinity	1	180		
Water	Infinity	555.08			
Phenylhydrazine	Infinity	1	238		

Yield: 52 → -24

Price / availability: 0

Safety: -10

Technical setup: Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique. Selected items: Instruments for controlled addition of chemicals; Pressure equipment, > 1 atm → -4

Temperature / time: Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h. Selected items: Room temperature, < 1h → 0

Workup and purification: Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography. Selected items: Classical chromatography → -10

EcoScale 52