RESEARCH REVIEW JOURNALS
Volume-02
Issue-10
October-2017

ISSN: 2455-3085 (Online)
RESEARCH REVIEW International Journal of Multidisciplinary
www.rrjournals.com

Microwave assisted protection and oxidative regeneration of carbonyl compounds using solid support

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ARTICLE DETAILS

Article History
Received: 05Oct 2017
Accepted: 25 Oct 2017
Published Online: 30 Oct 2017

Keywords
Microwave, solvent-free, quinolinium chlorochromate, phenylhydrazones, semicarbazones.

ABSTRACT

Protection of carbonyl compounds as phenylhydrazones and semicarbazones has been carried out using solid support in conjunction with microwave energy. Quinolinium chlorochromate along with same solid support has been further used for oxidative deprotection of phenylhydrazones and semicarbazones to carbonyl compounds.

1. Introduction

Protection of carbonyl compounds as phenylhydrazones and semicarbazones[1] is of great interest to synthetic organic chemists because of their stability and the ease of preparation. These are useful intermediates in organic chemistry and are utilized for isolation and purification of carbonyl compounds.[2] The most common method for the preparation of hydrazones or semicarbazones is the reaction of aldehydes or ketones with hydrazine and semicarbazide derivatives in the presence of base or acid as a catalyst[3] in addition to other known methods.[4]

Interest in regeneration of carbonyl compounds from their protected derivatives under mild conditions has also been growing in synthetic organic chemistry. Although the cleavage of oximes has engaged a lot of attention resulting in a multitude of reagents being employed for this purpose.[5] However, other similar imine derivatives such as semicarbazones and phenylhydrazones are often preferred over oximes for isolation and purification of naturally occurring carbonyl compounds thereby necessitating search for general protocols of cleavage of such derivatives. Most of the reported procedures used for this purpose involve hydrolysis under acidic and frequently stringent conditions, but are not satisfactory for acid sensitive compounds.[6-7] Several oxidative deprotection methods have been developed that have some advantages over the hydrolysis methods.[8] Little attention has been paid to the oxidative cleavage of phenylhydrazones and semicarbazones to corresponding carbonyl compounds and only a few reports are available.[9-10]

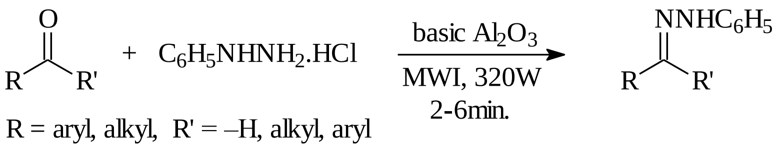
A survey of literature reveals that though there are numerous methods for deprotection of phenylhydrazones and semicarbazones,[11] most of them require drastic conditions, high temperature, long reaction times and expensive, toxic reagents. Heterogeneous reactions that are facilitated by supported reagents on various solid inorganic surfaces are receiving a lot of attention.[12] The advantage of these methods over conventional homogeneous reactions is that they provide greater selectivity, enhanced reaction rates cleaner products and manipulative simplicity. There has been a growing interest in the application of microwave radiations for high reaction rates and formation of cleaner products. Solvent-free reactions are especially appealing as they provide an ecofriendly system. Over the last two decades, the use of supported reagents under solvent-free conditions has opened up new and surprisingly useful approaches to chemistry.[13]

Due to our continuous endeavour to develop environmentally benign methods using solid-supports,[14-15] we here report an extremely convenient one-step synthesis of phenylhydrazones and semicarbazones from corresponding aldehydes and ketones on basic Al_2O_3 using microwave energy and explored a suitable method for the cleavage of C=N functionality. Taking a leaf out of quinolinium chlorochromate chemistry,[16] it was thought interesting to investigate its role for the oxidative regeneration of carbonyl compounds, from their imine derivatives such as hydrazones and semicarbazones.

2. Results and Discussion

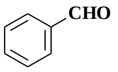
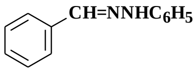
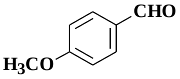
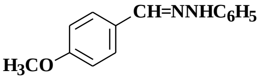
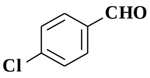
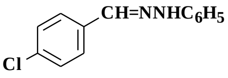
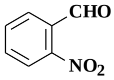
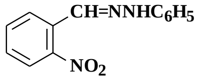
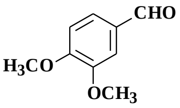
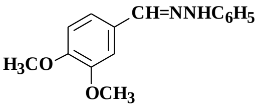
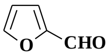
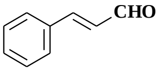
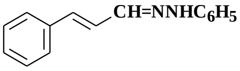
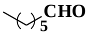
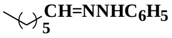
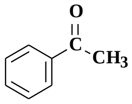
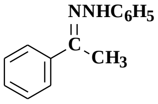
2.1. Protection of carbonyl compounds

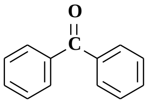
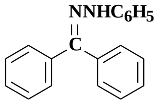
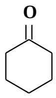
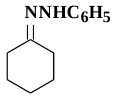
Scheme 1 represented the synthesis protocol used for the synthesis of phenylhydrozone from aldehydes and ketone analogues. Briefly, a mixture of carbonyl compound (1mmol) and phenylhydrazine chloride (1.5mmol) adsorbed on wet basic alumina were irradiated with microwave irradiation (320W). Cooling the reaction mixture followed with usual work-up procedure yielded the desired product.



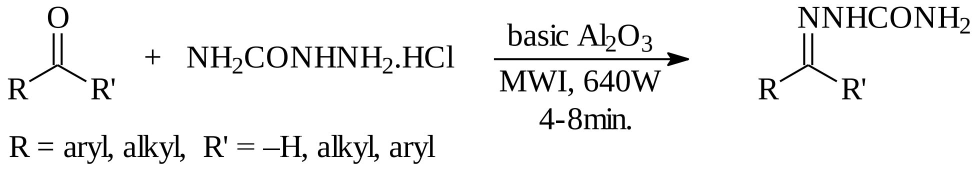
Scheme 1

Table 1: Synthesis of phenylhydrazones from aldehydes and ketones

Entry	**REACTANT**	**PRODUCT**	**MWI (320W)**		**m.p.**
			Time (min.)	**Yield (%)**	**(°C)**
1	 **1**	 **12**	3	89	155-158
2	 **2**	 **13**	2	96	119-121
3	 **3**	 **14**	4	78	125-127
4	 **4**	 **15**	5	87	152-155
5	 **5**	 **16**	3	91	58-60
6	 **6**	 **17**	4	82	97-99
7	 **7**	 **18**	4	66	165-168
8	 **8**	 **19**	4	64	--
9			3	74	104-107

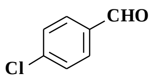
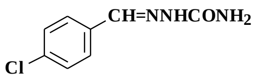
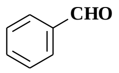
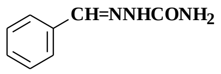
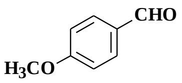
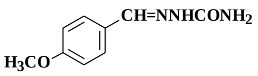
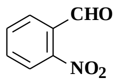
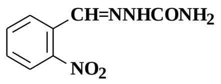
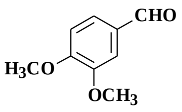
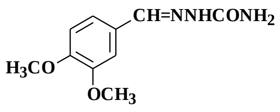
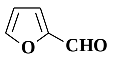
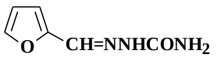
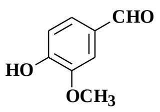
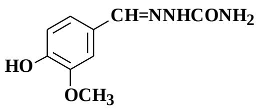
	9	**20**			
10	 **10**	 **21**	6	62	134-136
11	 **11**	 **22**	5	65	105-107

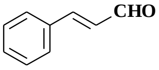
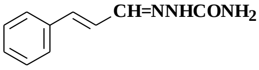
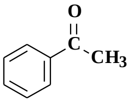
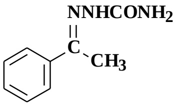
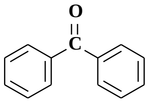
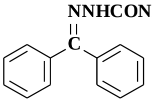
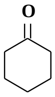
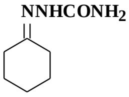
Semicarbazones were synthesized according to Scheme 2. Briefly, a mixture of carbonyl compound (1.0mmol) and semicarbazide hydrochloride (1.5mmol) were impregnated on wet basic alumina were irradiated with microwave irradiation (620W). Cooling the reaction mixture followed with usual work-up procedure yielded the desired product.



Scheme 2

Table 2: Synthesis of semicarbazones from aldehydes and ketones

Entry	**REACTANT**	**Product**	**MWI (620W)** **Time (min)**	 **Yield (%)**	**m.p. (°C)**
1	 **3**	 **23**	6	84	231-233
2	 **1**	 **24**	5	87	220-222
3	 **2**	 **25**	4	94	210-212
4	 **4**	 **26**	7	80	254-256
5	 **5**	 **27**	4	92	176-177
6	 **6**	 **28**	5	85	190-193
7			5	80	236-238

	35	29			
8			5	72	216-218
	7	30			
9			5	68	108-109
	8	31			
10			7	77	198-200
	9	32			
11			8	70	166-168
	10	33			
12			5	78	165-167
	11	34			

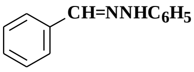
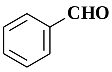
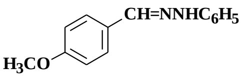
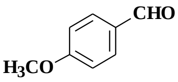
Satisfactory results were obtained in the reaction of a variety of aromatic aldehydes and ketones with phenylhydrazine hydrochloride and semicarbazide hydrochloride under solvent-free conditions in the presence of basic alumina as shown in Table 1 and 2. Acid-sensitive substrates, like furfural (**6**) and cinnamaldehyde (**7**) were also protected as hydrazones (**17,18**) and semicarbazones (**28**, **30**) in good yields without the formation of any side products. This method was advantageous as it employed heterogeneous catalyst and avoided the use of strong bronsted or lewis acid catalysis.

Hydrazones and semicarbazones were characterized by comparison of their physical data (IR spectrum and ^{1}H NMR spectrum) with known samples.[17] ^{1}H NMR spectrum of hydrazones showed the presence of a singlet between δ 7.8-8.1 due to R–C*H*=NNHPh while ^{1}H NMR spectrum of semicarbazones showed the presence of a singlet between δ 8.1-8.5 due to R–C*H*=NNHCONH$_2$. The singlet shifted a little upfield in aliphatic phenylhydrazones (δ 7.3) and semicarbazones (δ 7.6). IR spectra recorded prominent absorption bands between 1690-1630 (C=N) cm^{-1}. Further confirmation about the formation of hydrazones and semicarbazones was arrived at by the absence of singlet between δ 9.8-10.0 (–C*H*O) in the ^{1}H NMR spectra and also by the absence of IR absorption bands in the region 1715-1695 (C=O) cm^{-1}.

2.2. Deprotection of phenylhydrazones and semicarbazones

In a typical procedure, the reactants (1.0mmol) and QCC (1.2mmol) taken in dry DCM (5mL) impregnated on neutral Al$_2$O$_3$ were subjected to microwave irradiation in a domestic microwave oven at 480W for phenylhydrazones and at 800W for semicarbazones. The reaction mixture was cooled, diluted with DCM (3×10mL) and filtered. The filtrate was then passed through a silica column to remove QCC. Evaporation of the solvent *in vacuo* furnished the corresponding aldehydes and ketones in excellent to moderate yields (Table 3 and Table 4). The solvent-free reaction conditions employed avoids the risk of development of high pressures thus leading to explosions.

Table 3: QCC mediated deprotection of phenylhydrazones

Entry	Reactant	Product	MWI (480W)		Conventional Thermal Heating	
			Time (min.)	Yield (%)	Time (h)	Yield(%)
1			5	80	7	65
	12	1				
2			3	91	6	76

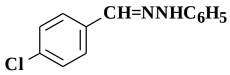
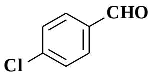
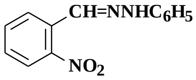
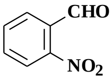
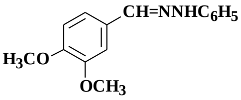
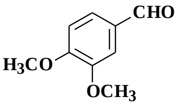
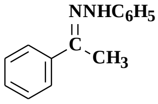
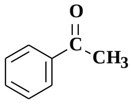
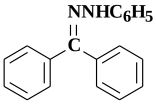
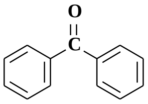
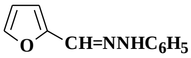
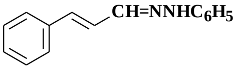
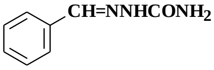
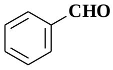
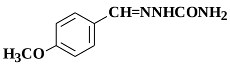
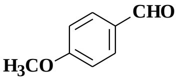
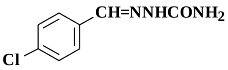
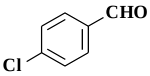
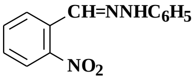
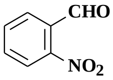
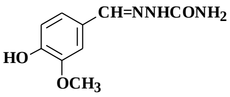
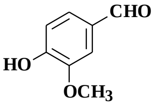
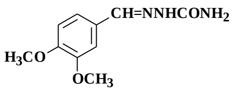
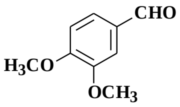
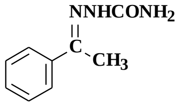
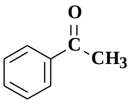
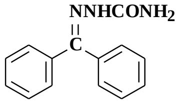
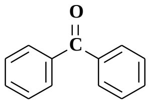
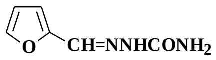
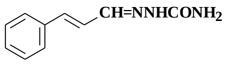
	13	**2**				
3			5	70	8	62
	14	**3**				
4			3	68	8.5	60
	15	**4**				
5			3	82	6	72
	16	**5**				
6			3	70	7	64
	17	**9**				
7			5	68	8	66
	18	**10**				
8		--	--	--	--	--
	19					
9		--	--	--	--	--
	20					

Table 4: QCC mediated deprotection of semicarbazones

Entry	Reactant	Product	MWI (800W)		Conventional Thermal Heating	
			Time (min.)	Yield(%)	Time (h)	Yield(%)
1			2	80	8	73
	24	**1**				
2			2	85	6	77
	25	**2**				
3			5	68	7	70
	23	**3**				
4			2	65	9	60
	26	**4**				
5			2	78	6	70

	29	**51**				
6	 **27**	 **5**	2	84	6	72
7	 **32**	 **6**	2	72	8	64
8	 **33**	 **7**	2	60	9	56
9	 **28**	--	--	--	--	--
10	 **30**	--	--	--	--	--

The structure of the regenerated carbonyl compounds was confirmed by spectral analysis. ^{1}H NMR spectra of aldehydes showed presence of singlet between δ = 9.8-10.0 (–C*H*O) and absence of peak in phenylhydrazones between δ 7.8-8.1 (R–C*H*=NNHPh) and in semicarbazones between δ 8.1-8.5 (R–C*H*=NNHCONH$_2$). IR spectrum of deprotected products showed absorption bands in the region 2750-2710 (–C*H*O) cm^{-1} and 1715-1695 (C=O) cm^{-1} which was absent in the IR spectrum of the substrates.

It is noteworthy that QCC, a selective oxidizing agent,[16] oxidizes primary alcohols in the presence of secondary alcohols. In the present study, QCC acts as a selective reagent for oxidative deprotection of aromatic semicarbazones and phenylhydrazones to the corresponding aldehydes and ketones. However, heterocyclic and α,β-unsaturated phenylhydrazones (**19**, **20**) and similar semicarbazones (**28**, **30**) remained inactive under similar conditions.

No over-oxidation of the aromatic aldehydes to carboxylic acids was observed. EWG at 2- and 4-positions (**13,14, 23, 26**) deactivates the derivatives sufficiently, hindering oxidative cleavage with QCC, resulting in lower yields of aldehyde (**3**, **4**). Reaction was found to be sluggish in the absence of alumina and no carbonyl compound was obtained using alumina alone even after prolonged heating in the microwave oven.

Effectiveness of other solid supports (Table 5) was also studied for the deprotection of phenylhydrazone of 4-methoxybenzaldehyde (**25**). Although deprotection occurred using other supports, best results were obtained only using neutral alumina as the supported reagent (Table 5). This may be due to variable adsorption tendencies of different solid supports.

Table 5: Effectiveness of other solid supports

Entry	Solid Support	Yield(%)
1	K-10	40
2	KSF	30
3	Flash Silica	60
4	Neutral Al$_2$O$_3$	88
5	None	0

3. Conclusion

In conclusion, selective and efficient microwave assisted preparation of phenylhydrazones and semicarbazones has been carried out using basic alumina. This methodology has an advantage of minimizing waste disposal and easy work-up, resulting in excellent yield of products. Further role of QCC was investigated for the oxidative regeneration of carbonyl compounds, from their imine derivatives such as hydrazones and semicarbazones under microwave irradiation, with no over-oxidation of the aromatic aldehydes to carboxylic acids.

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