

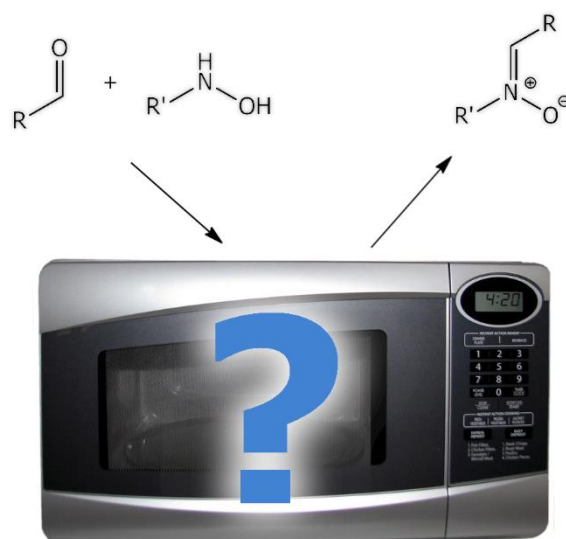
SciRad SCIENTIAE RADICES

Alternative Synthetic Protocols as a Way to Mask Unreliability in Organic Chemistry Research, Case of Nitrones

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Abstract: Microwave assisted reactions are extremely popular. Analysing articles tackling Microwave assisted syntheses of nitrones, some inconsistencies in used methods can be seen. Shortcoming found in the literature are hereby announced and discussed.

Keywords: Nitrones, Microwave radiation, Green chemistry

Received: 2024.10.09

Accepted: 2024.12.09

Published: 2024.12.16

DOI: 10.58332/scirad2024v3i4a05

Introduction

Among different methods used to promote desired reactions, mechanochemical approach, microwave and ultrasound irradiation are popular, as they often offer solvent free reaction conditions, quick reaction times, and high yields [1]. A closer look at the synthesis

of nitrones with alternative methods, has yet not been undertaken. While researching the topic a surprising amount of questionably described research was found. Hereby problems, encountered while analysing three articles undertaking topic of Microwave nitrone synthesis, are described.

Discussion

Example #1

In 2010 Hassan Valizadeh [2] conducted synthesis of 19 various nitrones in presence of ionic liquid, both in thermal (TH), and Microwave (MW) conditions. In the article the author shows structure of nitrones, the structure shown is incorrect, as acyclic aldonitrones as a rule occur in Z conformation [3].

The author claims that all products were characterized by elemental analysis, ¹H-NMR, ¹³C NMR, IR, and melting points. Melting points for all the obtained compounds are shown in the article. What is important, only 6 of 19 compounds prepared in the manuscript (labelled in the original paper: 3b, 3g, 3i, 3p, 3r, 3s) do have their spectral characteristics, and elemental analyses results disclosed.

According to the author the microwave aided reactions took between 3.5 and 5 minutes and gave yields between 93% and 99%. In the same article TH reactions took 2.5 to 3.5 hour yielding between 80% and 90%. The melting points measured stand in accordance with presented literature data, except for one compound (3m in the original article) where reported melting point is 13-116°C (sic). The reactions were performed by mixing 10 mmol of each: aldehyde, ionic liquid and N-substituted-N-hydroxylamine. What is important free hydroxylamines (R-NHOH; R= Ph, Bn, t-Bu, Me) were used in all the author's experiments [2]. For TH reaction no additional solvent was used, and all the reactions were conducted at 70°C.

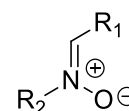
To better analyse nitrones prepared by H. Valizadeh [2]. All the nitrones described in the paper, and all nitrones possibly obtainable with used reagents, were plotted in table 1. Only 19 of 60 (ca. 32%) possible reactions are described in the article. It seems that reagent pairs were chosen randomly.

Creating such a wide array of compounds the author could have synthesised a better curated series and try to draw general conclusions on reactivity both in thermal and microwave conditions, eg. employing Hammett's constants and focusing only on benzaldehyde derivatives[4, 5].

As the author claims, all reagents were purchased from Merck. As for today (10th October 2024) only N-phenylhydroxylamine is available in pure form, N-methyl- and N-(tert-butyl)-N-hydroxylamine are available as either acetate or hydrochloride, while N-benzylhydroxylamine does not figure in the Merck online catalogue [6]. Making the syntheses problematic for reproduction, as the hydroxylamines must be either directly synthesised, or freed from their salts.

Table 1. Nitrones synthesised by H. Valizadeh [2] (given as labels in the original article) compared to all nitrones that could have been synthesised with reagents at play, cells where undescribed nitrones reside are greyed out.

R ₁	R ₂			
	Me	t-Bu	Ph	Bn
2-naphtyl	3a			3s
2-furyl	3d	3b		3r
2-pyridyl		3c		
4-pyridyl		3p		
2-thiophenyl ¹	3q			
4-cyanophenyl	3e			
4-methylphenyl	3f			
2-hydroxyphenyl			3g	
5-bromo-2-hydroxyphenyl		3n	3h	
2,3-dihydroxyphenyl			3i	
4-nitrophenyl			3j	
4-methoxyphenyl			3k	
4-hydroxy-3-methoxyphenyl		3l		
2-hydroxy-4-methoxyphenyl		3m		
2-hydroxy-5-methoxyphenyl		3o		



¹ as written by the Author, it probably should have been 2-thiophene

Example #2

In 2012 Cecilia Chavarria et al. [7] prepared 4 C-(hydroxyphenyl)-N-tert-butyl nitrones. Firstly, in the first scheme the authors have misspelled the t-Bu group formula, the mistake is benign and is not present in the rest of the article.

The authors tested 4 preparations in both MW and TH conditions. The thermal reactions were conducted for 3 h (compound labels in original article (OL): PBN, 5, 7) or 30 h (OL: 6), at 60°C (OL: PBN) or 78°C (rest of the compounds). The reactions were conducted in EtOH. The microwave reactions took between 10 and 30 minutes, the temperature ranged from 100°C to 150°C. The reactions were also conducted in the presence of ethanol as a solvent.

In cases of two prepared nitrones (OL: PBN, 5) MW procedure led to higher yields than the TH one. In one case (OL: 7) yields are comparable.

In case of one mixture (OL: 6) the thermal method led to higher yield (42%) than MW reaction at 100°C for 10 minutes (35%) and at 150°C for 30 minutes (no product observed)

The authors conducted both TH and MW reactions using similar protocol, aldehyde (1eq) and t-BuNH₂·HCl (1.1eq) were used. Sodium bicarbonate (1.1 eq) was used to free the hydroxylamine from its salt. There is however a weak spot in the preparative procedure. I strongly believe that it stems from inadvertence. Namely, the reaction mixture is evaporated, and the dry residue is taken into water, liquid-liquid extraction of the nitron with ethyl acetate follows. Unfortunately, nitrones tend to hydrolyse in water solutions [8]

The research paints MW synthesis as a method just as any other, more suited for preparation of some compounds than others.

Example #3

In 2017 Loredana Maiuolo et al. [9] tried to prepare 30 various nitrones based on 1-isatin and indanone analogues, under MW irradiation; of which 24 were successfully prepared. 15 ketones, and 5 various N-substituted-N-hydroxylamines hydrochlorides were used.

Focusing on comparison of the yields in the section, where the author optimised synthesis conditions (table 1 in the original article). Namely (*E*)-N-methyl-C-isatinylnitrone (OL: 4a), and (*Z*)-N-methyl-C-indanylnitrone (OL: 5a). As stated in the general procedure, great excess (100 % ÷ 200 %) of hydroxylamines was used, as compared to the reactions' stoichiometry.

In case of the (*E*)-N-methyl-C-isatinylnitrone (OL: 4a) authors tested MW conditions at 200 W, 400 W, and 600 W MW irradiation. The reactions took 10 ÷ 20 minutes, at 180°C. In this case, it is clear that, increasing MW irradiation power, at constant temperature, increases reaction's yield, while lowering excess of the hydroxylamine hydrochloride lowers reaction's yield.

Under the optimised conditions, yield of MW reaction is 80%, while in thermal conditions (RT, 24 h, 2 eq MeNH₂·HCl, 2 eq NaOAc, 1eq istatin, water:EtOH 1:1 as a solvent) yield is 70% of the nitron.

In case of the (*Z*)-N-methyl-C-indanylnitrone (OL: 5a), yields of MW reactions range 25 % ÷ 82 %. What is interesting, the yield benefits from lower MW irradiation power (400W instead of 600 W) and longer reaction times. The reaction in thermal conditions

realised at room temperature, with 2 eq both N-methyl hydroxylamine hydrochloride and sodium acetate, and water-ethanol 1:1 mixture as a solution; yielding 78 % of the nitron.

Unfortunately, neither of the thermal reactions seem to have been conducted at optimal conditions, and the yields can be undermined as probably unreliable. In a condensation of an N-alkyl hydroxylamine and an aldehyde, water forms as a side product [3, 8], thus the application of water-ethanol mixture as a solvent seems counterproductive. Authors when choosing solvent for the thermal reactions seem to be either oblivious to the reactions' stoichiometry or lack basic understanding of Le Chatelier's principle. Regardless, the yields of the thermal reactions seem to be sabotaged, by addition of water as a solvent.

Conclusion

Analysing only those three short research papers it is clear that the quality of research conducted by the authors vary widely from an honest comparison of reactions under different conditions [7], to solvent-sabotaged thermal reactions [9] and reagents chosen at random [2]. From the research articles discussed, it cannot be concluded that microwave conditions are a miraculous solution to facilitate nitrones' syntheses. The articles that clearly show microwave conditions as superior contain some methodical shortcomings.

Despite its popularity, microwave irradiation unfortunately is not a golden bullet solving all problems of a synthetic organic chemist; instead, it seems to be a method just as any other, useful for some preparations, while completely counterproductive for others. At the same time, I am afraid that the popularity of the technic may incentivise researchers to cherry-pick or otherwise dishonestly influence experimental results.

As observed in the case of nitrones and microwave irradiation, great care should be taken both while researching, and reviewing the "trendy" synthetic methods, to ensure high quality of the published results.

According to the previous analysis of the literature. To prevent bias in the conducted research on novel reaction methods it is advisable to:

- meticulously describe all the details of synthetic methods;
- rationalise why used reagents were selected, and why the model compounds were chosen;
- conduct both reference and novel reaction protocols in as similar conditions as possible, varying only one variable at once.

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