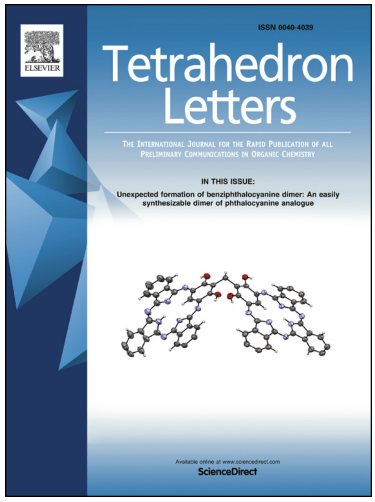

Facile microwave-assisted synthesis of thioformamides from isocyanides and carbon disulfide

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Facile microwave-assisted synthesis of thioformamides

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Sònia Abás, Ulrike Moens and Carmen Escolano*

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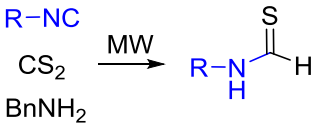

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ABSTRACT

A new, fast, solvent-free and efficient method is provided to prepare thioformamides by reacting isocyanides derivatives, carbon disulfide and benzylamine under microwave irradiation.

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Microwave-assisted organic synthesis (MAOS) is one of the cornerstones in modern synthetic organic chemistry. In fact, microwave instruments are becoming part of the equipment in numerous laboratories providing researchers with a new tool to enhance the arsenal of reactions. The increasing relevance of MAOS in accessing new entities providing efficient and cleaner procedures has been compiled in several reviews.[1]

Recently, we have contributed to MAOS's popularity describing a solventless access to (2-imidazolin-4-yl)phosphonates through a multicomponent reaction between diethyl isocyanomethylphosphonate, ketones and amines involving microwave irradiation in only 10 minutes at 40˚C.[2] The resulting 2-imidazolin compounds probed to be a structurally new family of high affinity imidazoline I_2 receptor ligands showing neuroprotective properties.[3] One of the key points for the success of the reaction was the divalent nature that exhibit isocyanides making possible reactions with a myriad of reaction partners of either electrophilic or nucleophilic character.[4]

Our interest in exploring isocyanides as an extremely useful class of organic compounds for synthetic chemistry, combined with our knowledge in the development of microwave assisted methodologies, prompted us to explore the preparation of thioformamides from isocyanides.

Thioformamides constitute a particular functional group embodying a high reactivity profile. They can be found as key intermediates in the synthesis of *N*-thioformyl peptides,[5] in the preparation of structurally diverse thioheterocycles some displaying fluorescence properties,[6] in the preparation of relevant heterocycles,[7] in the reaction with organometallic reagents giving access to diverse organic entities[8] and playing a starring role in the discovery of their physicochemical properties.[9]

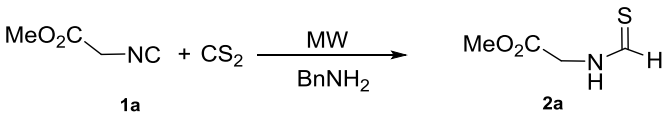
To the best of our knowledge few methods have been described for the synthesis of thioformamides being the most popular the reaction of isocyanides with thioacids.[10]

In this paper we add a new, efficient and safe methodology for the preparation of thioformamides using isocyanides and carbon disulfide, as the source of sulfur atoms, under microwave irradiation and in the absence of solvent.

Scheme 1. Reaction studied

As a proof of concept of our approach, a model reaction using methyl isocyanoacetate as substrate, carbon disulfide and benzylamine, was optimized. Most gratifyingly, the desired product **2a** was obtained in a 71% yield when an equimolecular mixture of reagents was irradiated in the microwave oven at 40ºC during 10 minutes. Neither excess of benzylamine (entry 2) nor excess of both benzylamine and carbon disulfide (entry 3) increased the yield. In order to rule out a catalytic role for the base, a substoichiometric amount of amine, 0.5 equivalents, was examined. In agreement with the putative mechanism of the reaction (see below), under this condition the yield dropped to 48% (entry 4). Finally, neither shorter reaction time (entry 5) nor higher reaction temperature increased the yield.

Table 1. Optimization of the reaction conditions.



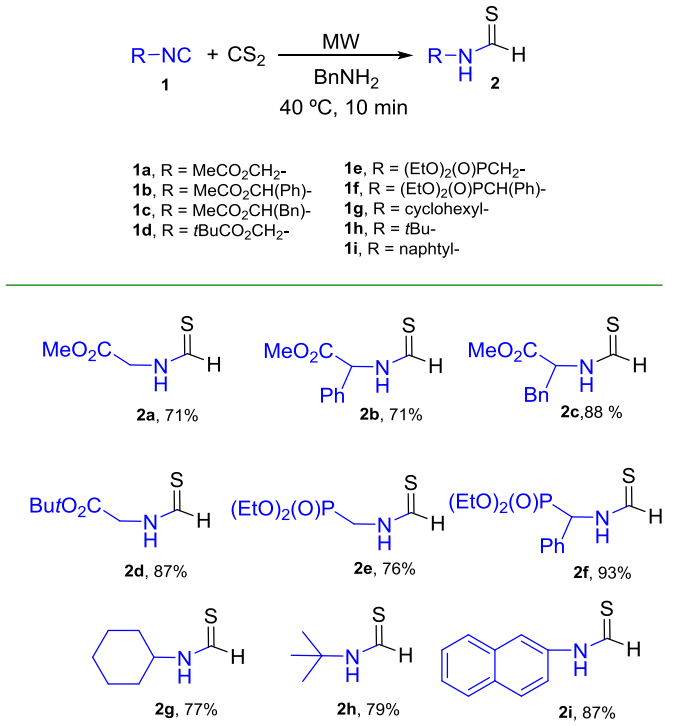
entry	$BnNH_2$ equivalents	CS_2 equivalents	MW conditions T/time	Yield[a] %
1	1.0	1.0	40ºC/10 min	71
2	1.5	1.0	40ºC/10 min	70
3	1.5	1.5	40ºC/10 min	70
4	0.5	1.0	40ºC/10 min	48
5	1.0	1.0	40ºC/5 min	54

[a]. Isolated yield of **2a**.

Therefore, the optimized conditions are microwave irradiation of a mixture of carbon disulfide, benzylamine and an isocyanide derivative in equimolecular quantities at 40 ºC for 10 min in the absence of solvent. With the standard conditions in hand, we surveyed the functional group compatibility and scope of the present microwave-assisted synthesis of thioformamides directing the efforts towards the structural diversity of the isocyanide compound.

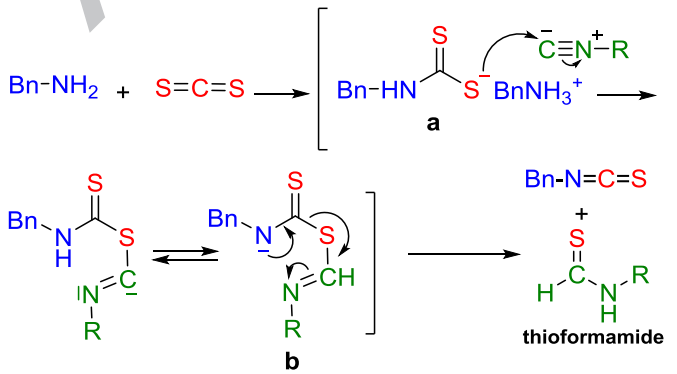
To this end, reactions with isocyanides substituted in the α position were undertaken. Thus, the use of methyl-α-phenylisocyanoacetate and methyl-α-benzylisocyanoacetate furnished thioamides **2b** and **2c** with 71 and 88% yields, respectively. Also the putative influence of the alkylgroup in the ester was evaluated by performing the reaction with *t*-butyl isocyanoacetate to furnish the product **2d** in an excellent 87% yield. Worthy of note, the reaction took place with a 76% yield when diethyl isocyanomethylphosphonate was used as reagent to produce **2e**. Similarly to the methyl ester series, the formation of the thioformamide **2f** also occurs in excellent yields, 93%, when diethyl α-phenylisocyanometylphosphonate, an isocyanide substituted in the α-position, was employed.

The use of alkyl isocyanide derivatives was also examined and cyclohexylisocyanide gave **2g** in 77% yield. When *t*-butylisocyanide, an isocyanide tetrasubstituted in the α-position was used, **2h** was isolated in 79% yield. Finally, the inclusion of aromatic isocyanides was undertaken and the naphtylisocyanide successfully afforded **2i** in 87% yield.[11]



Scheme 2. Synthesis of thioformamides **2a**-**2i**.

Of note, the reaction of carbon disulfide with amines has been applied in the last years for obtaining symmetrical thioureas.[12] However, in the presence of isocyanides the reaction evolved to give thioformamides. Taking into account that, in agreement with earlier reports,[13] one equivalent of benzylamine was needed for the formation of the dithiocarbamate salt **a**, which was observed within few minutes after the nucleophilic attack of benzylamine to carbon disulfide, a putative mechanism for this novel reaction is shown in Scheme 3. Very likely, under our usual reaction conditions, the intermediate **a** might attack the isocyanide to give the species **b** that would suffer fragmentation to deliver the final thioformamide and benzylisothiocyanate. Note that benzylisothiocyanate is produced in stoichiometric amount and therefore, the described procedure also covers an easy solvent free route to isothiocyanate derivatives. NMR spectra and HMRS probed the formation of intermediate **a** and benzylisothiocyanate. Considering the propose mechanism, with the sole exception of the sulfur atom, in the final thioamide all the atoms stem from the isocyanate reagent. Considering that a myriad of isocyanates are currently available, a very broad range of thioformamides can be accessed following this new methodology.



Scheme 3. Putative mechanism

To summarize, the work presented in this manuscript provides a mild, rapid and efficient method for accessing thioformamides compatible with a range of diversely substituted isocyanides. This method, contributes to enlarge the repertoire of useful reactions to be performed under microwave irradiation.

Acknowledgments

Financial support from the Spanish Ministry of Economy and Competitiveness MINECO: Project BQU2015-66030-R and SAF2016-77703-C2-1-R and Generalitat de Catalunya Grant 2014-SGR-01555 is grateful acknowledged.

A. Supplementary material

Detailed experimental procedures and copies of NMR spectra for all the new compounds are provided. Supplementary data associated with this article can be found, in the online version,

References and notes

1. (*a*) Kruithof A, Ruijter E, Orru RVA. Microwaves in Organic synthesis. A. de la Hoz, A. Loupy. Ed.; Wiley 2002; p. 1099;
(*b*) Kappe CO, Dallinger D. *Mol. Divers*. 2009; 13: 71-193;
(*c*) Caddick S, Fitzmaurice R. *Tetrahedron*. 2009; 65: 3325-3355.
(*d*) Kruithof A, Ruijter E, Orru RVA. *Curr. Org. Chem*. 2011; 15: 204-236;
(*e*) Moseley JD, Kappe CO, *Green Chem*. 2011; 13: 794-806;
(*f*) Majumder A, Gupta R, Jain A, *Green Chem. Lett. Rev*. 2013; 6: 151-182.
2. Abás S, Estarellas C, Luque FJ, Escolano C. *Tetrahedron*. 2015; 71: 2872-2881.
3. Abás S, Erdozain AM, Keller B, Rodríguez-Arévalo S, Callado LF, García-Sevilla JA, Escolano C. *ACS Chem. Neurosci*. 2017; DOI: 10.1021/acschemneuro.6b00426.
4. (*a*) Gulevich AV, Zhdanko AG, Orru RVA, Nenajdenko VG. *Chem. Rev*. 2010; 110: 5235-5331.
(*b*) Tobisu M, Chatani N. *Chem. Lett*. 2011, 40, 330-340.
(*c*) Isocyanide Chemistry Applications in Synthesis and Materials Science. Weinheim: Wiley-VCH; 2012.
(*d*) Bode ML, Gravestock D, Rousseau AL. *Org. Prep. Proced. Int*. 2016; 48: 89-221.
(*e*) Wang Y, Kumar RK, Bi X. *Tetrahedron Lett.* 2016; 57: 5730-5741.
(*f*) Giustiniano M, Basso A, Valentina M, Massarotti A, Novellino E, Tron GC, Zhu J. *Chem. Soc. Rev*. 2017; 46: 1295-1357.
5. (*a*) Yuan Y, Zhu J, Li X, Wu X, Danishefsky SJ. *Tetrahedron Lett.* 2009; 50: 2329-2333.
(*b*) Fowler BS, Mikochik PJ, Miller SJ. *J. Am. Chem. Soc*. 2010; 132: 2870-2871;
6. (*a*) Murai T, Hori F, Maruyama T. *Org. Lett*. 2011; 13: 1718-1721;
(*b*) Yamaguchi K, Murai T, Hasegawa S, Miwa Y, Kutsumizu S, Maruyama T, Sasmori T, Tokitoh N. *J. Org. Chem*. 2015; 80: 10742-10756.
7. Zou JP, Zeng RS, Lu ZE, Chen KQ. *Trends in Heterocycl. Chem.* 2001; 7: 107-116.
8. (*a*) Murai T, Asai F. *J. Am. Chem. Soc*. 2007; 129: 780-781.
(*b*) Murai T; Kazuki U, Narengerile K. *J. Org. Chem*. 2009; 74, 5703-5706.
(*c*) Murai T, Hori R. *Bull. Chem. Soc. Jpn*. 2010; 83: 52-57.
(*d*) Murai T, Matsushita K, *Phosphorus Sulfur Silicon Relat. Elem*. 2011; 186: 1094-1103.
(*e*) For a review, see: Murai T, Mutoh Y. *Chem. Lett*. 2012; 41: 2-8.
(*f*) Wei J, Liu L, Zhan M, Xu L, Zhang WX, Xi Z. *Angew. Chem. Int. Ed*. 2014; 53: 5634-5638.
(*g*) Murai T, Mutoh N. *J. Org. Chem*. 2016; 81: 8131-8134.
9. Hutton DA, Shang J, Wille U. *Chem.- Eur. J*. 2016; 22: 3163-3169.
10. (*a*) Chupp JP, Leschinsky KL, J. Org. Chem. 1975; 40: 66-71.
(*b*) Reference 5a.
(*c*) Stockdill JL, Wu X, Danishefsky SJ. *Tetrahedron Lett*. 2009; 50: 5152-5155.
(d) Ramazani A, Joo SW, Nasrabadi FZ. *Turk. J. Chem*. 2013; 37: 405-412.

11. Compound **1i** is a solid, therefore, in the preparation of **2i** the use of ethanol was required.
12. Jangale AD, Kumavat PP, Wagh YB, Tayade YA, Mahulikar PP, Dalal DS. *Synth. Commun*. 2015; 45: 236-244.
13. Munch, H, Hansen JS, Pittelkow M, Christensen JB, Boas U. *Tetrahedron Lett*. 2008, 49, 3117-3119.

Microwave assisted method to access thioformamides
A mechanism is proposed
Different substituted thioformamides prepared in good yields
Isocyanides and carbon disulfide furnish without solvent thioformamides