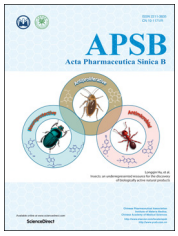
Acta Pharmaceutica Sinica B 2017;7(4):523–526

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



SHORT COMMUNICATION

The reaction of cinnamaldehyde and cinnam(o)yl derivatives with thiols

Alessandro Autelitano[a], Alberto Minassi[a], Alberto Pagani[a], Orazio Taglialatela-Scafati[b,*], Giovanni Appendino[a,]**

[a]*Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale, Largo Donegani 2, Novara 28100, Italy*
[b]*Dipartimento di Farmacia, Università di Napoli Federico II, Via Montesano 49, Napoli 80131, Italy*

Received 18 April 2017; revised 1 June 2017; accepted 2 June 2017

KEY WORDS

Cinnmaldeyde;
Michael addition;
Electrophiles;
Conjugation;
Cysteamine;
Chalcones

Abstract Spurred by the alleged relevance of the thia-Michael reaction in the bioactivity of various classes of cinnam(o)yl natural products and by the development of a quick NMR assay to study this reaction, we have carried out a systematic study of the "native" reactivity of these compounds with dodecanethiol and cysteamine as models, respectively, of simple thiols and reactive protein thiols that can benefit from iminium ion catalysis in Michael reactions. Cinnamoyl esters and amides, as well as cinnamyl ketones and oximes, did not show any reactivity with the two probe thiols, while cinnamaldehyde (**1a**) reacted with cysteamine to afford a mixture of a thiazoline derivative and compounds of multiple addition, and with aliphatic thiols to give a single bis-dithioacetal (**6**). Chalchones and their vinylogous C5-curcuminoid derivatives were the only cinnamoyl derivatives that gave a thia-Michael reaction. From a mechanistic standpoint, loss of conjugation in the adduct might underlie the lack of a native Michael reactivity. This property is restored by the presence of another conjugating group on the carbonyl, as in chalcones and C5-curcuminoids. A critical mechanistic revision of the chemical and biomedical literature on cinnamaldehyde and related compounds seems therefore required.

*Corresponding author. Tel.:+39 081678509; fax: +39 081678552.
**Corresponding author. Tel.:+39 0321375744; fax: +39 0321375744.
E-mail addresses: scatagli@unina.it (Orazio Taglialatela-Scafati); giovanni.appendino@uniupo.it (Giovanni Appendino).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2017.06.005

1. Introduction

Cinnamon (*Cinnamomum verum* J. S. Presl. and *C. aromaticum* Nees.) is one of the oldest spices, being already mentioned in the early Chinese medical treatises and in the old Sanskrit texts[1]. The trade of cinnamon from India to the Mediterranean area is documented from the beginning of the Egyptian civilization[1], and cinnamon quills and cinnamon oil are nowadays extensively used in flavoring, perfumery, beverages, and medicines. The main constituent of cinnamon oil (up to over 80%) is cinnamaldehyde (**1a**, Fig. 1), a pleiotropic bioactive agent of current interest as anti-diabetic and antifungal agent[2]. Cinnamaldehyde is a reactive compound, whose chemical "exuberance" is responsible not only for the many beneficial effects associated to cinnamon, but also for allergic reactions to cinnamon-containing perfumes, cosmetics, and sweets (cinnamon buns, cinnamon cereals and apple cakes)[3]. Severe allergic reactions of the skin and mucous membranes have also been observed in baking personnel and in workers processing cinnamon[3], and because of this allergic potential, the acceptable daily intake (ADI) of **1a** has been set at the rather low value of 1.25 mg/kg[4]. Cinnamaldehyde is also extensively used in detergents and household cleaner, and is, in an industrial perspective, a high production volume (HPV) material, with an estimated consumption of 1000 metric tons per year[3].

The allergic reactions to cinnamaldehyde have been related to its Michael reactivity and its ability to form stable adducts with proteins. A similar mechanism has been proposed to explain the capacity of **1a** to activate TRPA1, the mustard oil receptor, by alkylation of the thiol-rich ankyrin moiety of this ion channel[5]. There is little doubt that cinnamaldehyde is capable to react with thiol groups, and this compound has, indeed, been extensively used in biochemical studies as a thiol-active agent, just like iodoacetamide or phenylarsine oxide[6]. However, the precise mechanism by which cinnamaldehyde traps thiols is unclear. The reaction of cinnamaldehyde with thiols has been considered the archetypal conjugated addition reaction that does not take place to any significant extent in the absence of secondary or primary amine[7], establishing itself as a benchmark reaction to evaluate the performance of organocatalysts[8]. In accordance with this view, mutation studies with biological targets of **1a**, including TRPA1, have highlighted the relevance of the formation of an imine with an arginine residue as a prelude to the Michael addition[9]. On the other hand, formation of hemithioacetals and not of Michael adducts was observed in the reaction of cinnamaldehyde and thiols in ionic liquids[10], and spontaneous Michael reaction with thiols has also been reported, although the adducts could be characterized only after derivatization[11]. Confusion also exists in the Michael reactivity of cinnamoyl derivatives of general formula **1**, that have been assumed, mainly in the biomedical literature, to behave as Michael acceptors without any clear demonstration of the actual occurrence of this reaction[12]. In the case of chalcones, formation of unstable Michael adducts, quickly reverting to the starting enones, has also been reported[13].

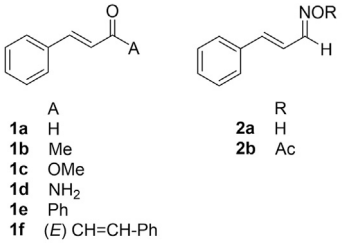


Figure 1 Chemical structures of cinnamaldehyde (**1a**), methylcinnamylketone (**1b**), methylcinnamate (**1c**), cinnamide (**1d**), chalcone (**1e**) and dicinnamylketone (**1f**), the oxime of cinnamaldehyde (**2a**) and its acetyl derivative (**2b**).

Cinnamoyl derivatives might as well give Michael adducts under a judicious selection of catalysts, promoters, and pHs, but there is a surprising lack of information on the "native", uncatalyzed reactivity of these compounds with thiols. Given the biomedical relevance of cinnamoyl derivatives in drug discovery and nutrition[14], we have investigated the behavior of this class of compounds with two probe thiols, the odorless dodecanethiol as a model of a simple thiol, and cysteamine as a model of reactive thiol in a protein that can benefit from imine catalysis[15].

2. Results and discussion

Cinnamaldehyde is an ambident electrophile, in principle capable to react with thiols both at the carbonyl and at the β-carbon. In practice, neither of these reactions is supposed to take place without Lewis acid catalysis (attack to the carbonyl and formation of the dithioacethal) or organocatalysis (pre-formation of an iminium ion followed by Michael addition)[7,8]. In terms of frontier molecular orbitals, these maneuvers decrease the LUMO energy and remodulate its coefficients, increasing its value on the carbonyl (ipso) carbon (Lewis acid catalysis) or on the β-carbon (organocatalysis)[7]. In accordance with this view, reaction of cinnamaldehyde with cysteamine in DMSO (cysteamine assay, Fig. 2) gave as a major compound the thiazoline adduct **3** (Fig. 3), resulting from imine formation at the carbonyl group and Michael addition at the conjugated double bond. Several other compounds were also formed, resulting from the multidentate reactivity of cinnamaldehyde, and dilution with $CDCl_3$ did not revert their formation. Compound **4a** (Fig. 3) was the result of the intermolecular version of the process generating the thiazoline **3**, with one molecule of cysteamine (or its disulfide oxidation product) trapping the carbonyl and the other one the olefinic double bond, while compounds **5a** and **5b** (Fig. 3) resulted from the reaction of two molecules of cinnamaldehyde with three molecule of cysteamine. The formation of these compounds shows that cinnamaldehyde acts as a multiple trap for "active" thiol groups, being capable

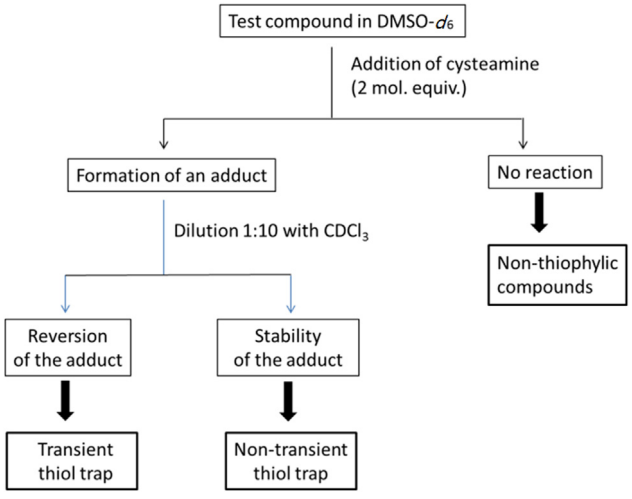


Figure 2 Classification of thiol-trapping compounds according to the cysteamine assay[15].