



Direct chemical derivatization of natural plant extract: straightforward synthesis of natural plant-like hydantoin



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ABSTRACT

The direct chemical derivatization of natural plant extracts that would enable the straightforward synthesis of natural plant-like molecules seemed to be far from reality due primarily to the inherently complex chemical property of the extract. After model studies, the envisioned derivatization was realized under the rationally designed Bucherer–Bergs reaction conditions to afford unnatural hydantoin with tetrasubstituted carbon from the ethyl acetate extract of *Curcuma zedoaria*. The reaction proceeded with enough chemoselectivity to identify the desired product from the mixture by the reliable guidance of spectroscopic analyses.

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Natural plant products and their derivatives have played pivotal roles in both pharmaceutical and agrochemical discoveries. In fact, many approved pharmaceuticals and agrochemicals as well as their candidates have their origin in natural plant products.¹ In addition to their successes and potentials as origins, the natural plant extract itself has been used as a ‘chemical library’, that is, an assembly of molecules rich in structural diversity for biological assay in early drug discovery. Thus, natural plant products have long been and will continue to be important sources of valuable chemicals. Despite such continuous demand for new natural plant products or related molecules, the chances of finding novel biologically active compounds have become more difficult.² It is partially because most of them have already been described in the literature especially for plants with pronounced pharmacological activities, but more importantly because their discoveries still continue to depend on a more or less accidental process regardless of whether guided by biological activities or not. Chemists are now enlisting combinatorial chemistry,³ diversity-oriented synthesis,⁴ and enzyme engineering⁵ as alternative approaches toward creating natural plant product-like molecules in combination with acquiring structural diversity. It should be strongly emphasized that the advances in these methodologies have opened up robust solutions for the designated production of natural plant product-like

molecules. Here, as an attractive alternative in terms of practical operation and scope, it would be quite reasonable that direct chemical derivatization of natural plant product extracts could provide another approach to construct natural plant product-like molecules. Furlan and co-workers have recently reported the first example of the direct chemical derivatization of natural plant extracts, where a novel unnatural alkaloid was successfully obtained.⁶ Since then, direct chemical derivatization of natural plant extracts has become a tool for creating natural plant product-like molecules, and been excellently applied to ammonolysis,⁷ sulfonylation,⁸ bromination,⁹ and epoxidation and subsequent ring-opening reaction¹⁰ of natural plant extracts.¹¹

Despite the advent of methodology for direct chemical derivatization of natural plant extracts, its application has been only rarely examined for several reasons. Firstly, it is because the inherently complex nature of extracts leads to the unpredictable results on the occasion of their derivatization so that the reaction system strongly demands the compatibility with the composition of extracts. In addition, a previous report has also described the difficulties in identifying the desired products from derivatized extracts.¹⁰ This was attributed to increasingly complicated profiles of derivatized extracts resulting from unwanted or uncontrollable side reactions and remaining reagents after general work-up. As a result, direct chemical derivatization of natural plant extracts, with its successes, still looks quite difficult. Therefore, further research is needed to provide the proof of concept and improve its scope and practicality.

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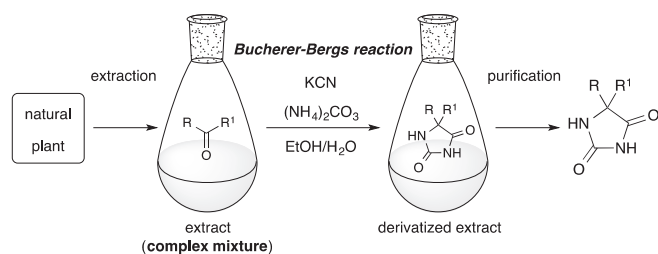
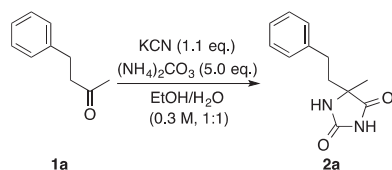


Figure 1. Direct chemical derivatization of natural plant extract.

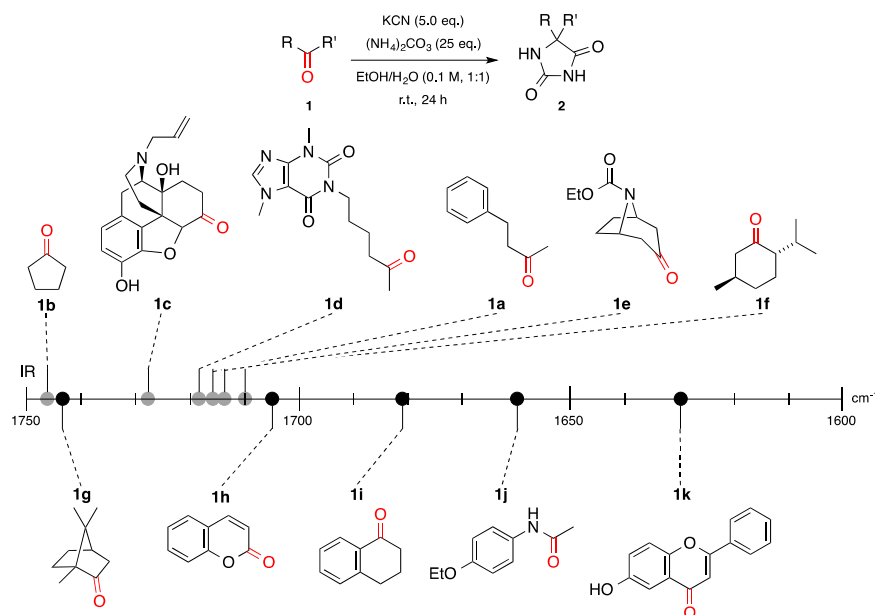
Table 1
Optimization of reaction conditions



Entry	Temp	Time (h)	Yield (%)
1	60 °C	4	97
2	rt	24	Quant.
3 ^a	rt	24	98

^a Performed with 5.0 equiv of KCN and 25 equiv of $(\text{NH}_4)_2\text{CO}_3$ in EtOH/ H_2O (0.1 M, 1:1).

Table 2
Scope and limitations



Entry	1	$[\nu(\text{C}=\text{O})]$ (cm^{-1}) ^a	2	Yield (%)	Entry	1	$[\nu(\text{C}=\text{O})]$ (cm^{-1}) ^a	2	Yield (%)
1	1b	1746 (neat)	2b	95	7	1g	1743 (KBr)	2g	N. R. ^b
2	1c	1727 (KBr)	2c	85	8	1h	1705 (KBr)	2h	N. R. ^b
3	1d	1719 (KBr)	2d	92	9	1i	1681 (neat)	2i	42 ^c
4	1a	1716 (neat)	2a	98	10	1j	1660 (KBr)	2j	N. R. ^b
5	1e	1714 (neat)	2e	85	11	1k	1630 (KBr)	2k	N. R. ^b
6	1f	1710 (neat)	2f	90					

^a Wave number of C=O (shown in red) stretching vibration in IR spectra.

^b No reaction occurred and the substrate was recovered.

^c The substrate was recovered.

Considering these challenges in direct chemical derivatization of natural plant extracts, the following requirements must be met: (1) the derivatization should take place in a chemoselective manner to minimize the unpredictable complication of the reaction system under reaction conditions. (2) The desired product should be easily detected by and purified with the reliable guidance of spectroscopic and analytical methods. (3) Then this becomes much easier especially when the constructed motif is scarce in the natural sources. With these in mind, it was thought that our envisioned story toward direct chemical derivatization of natural plant extracts could be realized by the Bucherer-Bergs four component reaction (Fig. 1).¹² Under the Bucherer-Bergs reaction conditions, the electrophilic carbonyl group is transformed into a hydantoin motif (imidazolidine-2,4-dione), beginning from the nucleophilic attack of ammonia to the electrophilic carbonyl group. Although a carbonyl group is known to be one of the most abundant functionalities in natural plant extracts,⁶ targeted electrophilic ketones can be certainly differentiated from other carbonyl groups during the course of the reaction with the nucleophile, then this would overcome the complication and realize the chemoselective derivatization even in the complex reaction system. The existence of electrophilic ketones could be estimated by the measurement of C=O stretching vibration in the IR spectra as shown below. Moreover, the product hydantoin is much more polar than the starting ketone and this will be beneficial to identify the desired hydantoin when the reaction is applied to the extracts comprising the molecules with low polarity. Although some naturally occurring hydantoin were identified from microbial¹³ and marine¹⁴ organisms, to our knowledge there has been no report in isolating them from

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