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MILD AND EFFECTIVE SOLVENT FREE SYNTHESIS OF 5-SPACER MONOCARBONYL CURCUMIN ANALOGUES

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ABSTRACT

Curcumin (1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one) has been reported to possess multifunctional bioactivities with low toxicity. Unfortunately, the biological application of curcumin has been significantly limited by its poor bioavailability. Till now, various attempts are being made to overcome these limitations to obtaining novel biologically active curcumin, and many analogues of curcumin have been designed and synthesized. In all of those analogues, a series of mono-carbonyl curcumin analogues deleting the β-diketone draw our attention. Since the seven-carbon β-diketone linker in curcumin may be responsible for its instability, the series of mono-carbonyl curcumin analogues deleting the β-diketone may be potential prodrug withimproved pharmacokinetic and pharmacodynamic properties. This review just focuses on these more stable mono-carbonyl analogues of curcumin, and shows the new class of active structure by introducing the synthesis and anticancer activity of them.

Keywords: Curcumin; Solvent free; 5-Spacer Curcumin Analogues: Claisen-Schmidt reaction

INTRODUCTION

Curcumin [1, 7-bis-(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione]is a yellow compound isolated from the rhizome of the herb Curcuma longa L., which has been used for centuries as a dietary pigment, spice, and traditional medicine in India. It is reported that curcumin is safe when taken orally up to 12 gm. per day without any toxic effect[1] . Until now, various studies have shownthat curcumin contain multifunctional pharmacological properties.[2, 3] The medical history of curcumin, particularly in Asia, found to be centuries-old traditional ayurvedic practice to modern times. In the current environment that combines medicinal

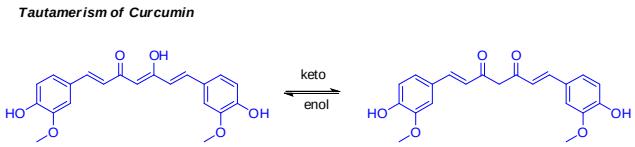
chemistry, pharmacology, biochemistry and molecular biology. The modern researcher proves that curcumin molecule can serve as an anti-cancer,antioxidant, antifungal, anti-inflammatory antimicrobial. The extended list includes protection for heart ailments, arthritis, wound healing, depression and Alzheimer's disease among many others. It is not surprising, then, that considerable health care research has been devoted to testing the efficacy of curcumin as a pure agent, in various formulations and in combination with other proven drugs.

The Claisen-Schmidt reaction (crossed-aldol reaction) is a condensation reaction of aldehydes and carbonyl compounds leading to α-hydroxycarbonyl compounds and it has played an important role insynthetic organic chemistry [4-6]. Followed by dehydration of the β-hydroxycarbonyl compoundsafford α-alkylidene or α-arylidene compounds. Although studies on the Claisen-Schmidt reaction have been focused on α-alkylidene and α-arylidene carbonyl compounds, interest in α,α'-bisalkylidene andα,α'-bisarylidene-carbonyl compounds is increasing.

In this present study we used mild base Calcium Hydroxide for the synthesis of bisalkylidene and bisarylidene at mild condition. As five spacer monocarbonyl curcumin analogues are promising precursor for many heterocyclic curcumin analogues. Our interest focus on finding new mild and simple but efficient way to synthesis of monocarbonyl curcumin analogues for its pharmacological importance.

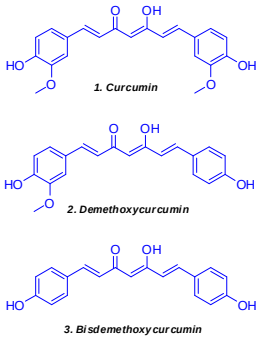
STRUCTURE OF NATURAL CURCUMIN

Figure 1.



Curcumin isolated from turmeric, once believed to be a single component showing keto-enol tautamersim as in Figure 1, but later work shown that curcumin is a mixture of three closely related species, Figure 2. Theydiffer by the methoxy group attached to the phenolic rings, Curcumin-2 ischemically demethoxy curcumin (DMC) and Curcumin-3 is bis-demethoxycurcumin (BDMC). Curcumin and other related components are generally calledby the name Curcuminoids.

Figure 2



MATERIALS AND METHODS

All chemicals were purchased from S.D.Fine and Loba Company. They were distilled before use and stored over a drying agent where necessary. IR spectra were recorded with a Shimadzu FTIR-408 spectrophotometer as KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker 400 AC spectrometer in $CDCl_3$ as a solvent at room temperature. Curcuminoids were isolated by HPLC apparatus. TLC was performed by the use of Merck's silica gel.

GENERAL EXPERIMENTAL PROCEDURE

Aliphatic Ketone (1eq.)and Aromatic aldehydes (2 Eq.) were taken in mortar powder of calcium hydroxide were added and pestle vigorously for 30 min. and kept aside at room temperature. On completion of reaction (TLC) water was added then filters wash with water recrystalised from appropriate solvent to obtain pure monocarbonyl curcumin analogues.

General Scheme 1.

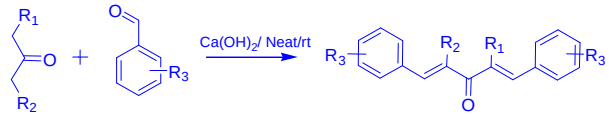


Table 1.Substituted ketone and aldehyde used in the reaction scheme 1

Sr. No.	R_1	R_2	R_3	M.P (°C)	Yield
1	CH_3	CH_3	H	92-98	97%
2	CH_3	CH_3	o-Cl	118-119	93%
3	CH_3	CH_3	p-Cl	191-192	95%
4	CH_3	CH_3	p-Me	176-177	96%
5	CH_3	CH_3	p-OMe	129-130	97%
6	Cyclohexanone	-----	p-Me	165-166	94%
7	Cyclohexanone	-----	m-Cl	105-106	92%
8	Cyclohexanone	-----	H	117-119	91%
9	Cyclohexanone	-----	o-NO_2	155-157	86%
10	Cyclopentanone	-----	H	185-186	96%
11	Cyclopentanone	-----	o-Br	165-166	97%
12	Cyclopentanone	-----	p-Me	181-182	96%
13	Cyclopentanone	-----	p-OMe	209-210	97%

RESULT AND DISCUSSION

We optimized reaction condition by varying amount of catalyst (Calcium Hydroxide) from 0.5 equivalents to 5 equivalents. Best result was observed with 2 mole of catalyst, by on adding excess catalyst does not much effect on yield of product. Continuous grinding of pestle is also observed as playing key role for enhancing yield of product. Putting reaction aside with poor grind markly reduce yield of reaction.

REFERENCES

1. NCI, DCPC, J. Cell Biochem. 1996, 26S, 72
2. Jagetia, G. C.; Aggarwal, B. B. J. Clin. Immunol. 2007, 27, 19.
3. Kumar, A. P.; Aggarwal, B. B.; Bharti, A. C. Anticancer Res. 2003, 23, 363
4 Nielsen, A.T.; Houlihan, W.J. Organic Reactions. In The Aldol Condensation; Adams, R.,Blatt, A.H., Boekelheide, V., Cairns, T.L., Cram, D.J., House, H.O., Eds.; J. Wiley & Sons: New York, NY, USA, 1968; Volume 16, pp. 1–438.
5 Mukaiyama, T. Organic Reactions; Dauben, W.G., Ed.; J. Wiley & Sons: New York, NY, USA,1982; Volume 28, pp. 203–331.
6 Heathcock, C.H. Comprehensive Organic Synthesis; Trost, B.M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Volume 2, pp. 133–179