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An effective method for bisphosphonate moiety inserting into O–H bond of carboxylic acids by Cu (II) catalyst

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ABSTRACT

In this study we developed a novel copper-catalyzed O–H insertion of tetraethyl diphosphonodiazomethane into carboxylic acids, providing a simple method to link bisphosphonates to compounds containing carboxyl group. Moreover, a novel bone-targeting prodrug of naproxen was synthesized according to this new methodology, and the preliminary evaluation indicated that the prodrug exhibited excellent bone affinity *in vitro*.

Introduction

In the human body, bone tissue is distinguished from the other tissues due to the presence of a massive mineral phase, i.e., biological apatite.[1] Bisphosphonates (BPs), discovered in 1960s, are analogs of pyrophosphate. By replacing the oxygen atom of P—O—P in pyrophosphate, bisphosphonates show enzymatically stability.[2] It was found that BPs had high binding affinity for hydroxyapatite, an analog of bone mineral. The targeting capability of bisphosphonates facilitated their accumulation in bone cells, particularly the osteoclast, hence making them good bone disease drug candidates.[3] To date, there are at least eight clinical bisphosphonate drugs that are widely used for treating bone diseases such as osteomyelitis, osteoporosis, Paget's disease and primary or metastatic bone tumors (Fig. 1).[4–8]

Despite their therapeutic use, BPs are also used as bone-targeting moieties (Fig. 2).[3] Inserting bisphosphonate to a drug molecules is a promising strategy to deliver efficient drug to bones. For instance, linking methotrexate, an antineoplastic drug, with a bisphosphonate moiety through a aliphatic chain could efficiently deliver the drug to target regions.[9] Moreover, the conjugate of ciprofloxacin with BPs through a long linker could enable high bone-antimicrobial concentration without increasing the administered dose for the treatment of osteomyelitis.[5,10] Furthermore, BP-diclofenac complex exhibited enhanced bone accumulation *in vivo* compared with the parent drug diclofenac.[11] In addition, our group previously reported an anticancer prodrug conjugating melphalan to a gem-bisphosphonate moiety through an amide linker. The chimera compound also showed a high affinity to hydroxyapatite *in vitro*, indicating a potential application in treating bone tumor.[12]

However, the molecules above utilized a long chain to link bisphosphonate with parent drugs, and were not easily accessible in synthesis. Thus, chemical modifications on these drugs could be challenging. In the present work, we aimed to find a straightforward approach that could minimize the molecule weight or shorten the linkage without losing the bone-targeting potency. We came to focus on the carboxyl, which was a common group in many drugs and could be linked to BPs directly.

Naproxen, a non-steroidal anti-inflammatory drug (NSAID), could conjugate with BP through ester bond to form a simple bone-targeting prodrug, which may have a potential application in treatment of osteoarthritis.[13] To our delight, it was found that the reaction of carboxyl with diethyl diazomalonate demonstrated the possibility to synthesize the target compound.[14] Moreover, to our best knowledge, the esterification reaction of carboxylic acids with tetraethyl diphosphonodiazomethane has not been reported yet. Herein, we reported a viable method to insert bisphosphonate moiety into O—H bond of carboxylic acids catalyzed by copper (II).

Results and discussion

To identify the optimal reaction conditions, benzoic acid **1a** and tetraethyl diphosphonodiazomethane **2** were selected as model

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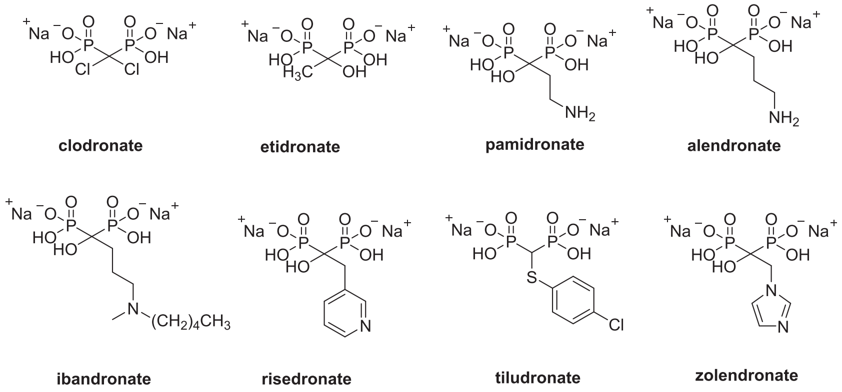
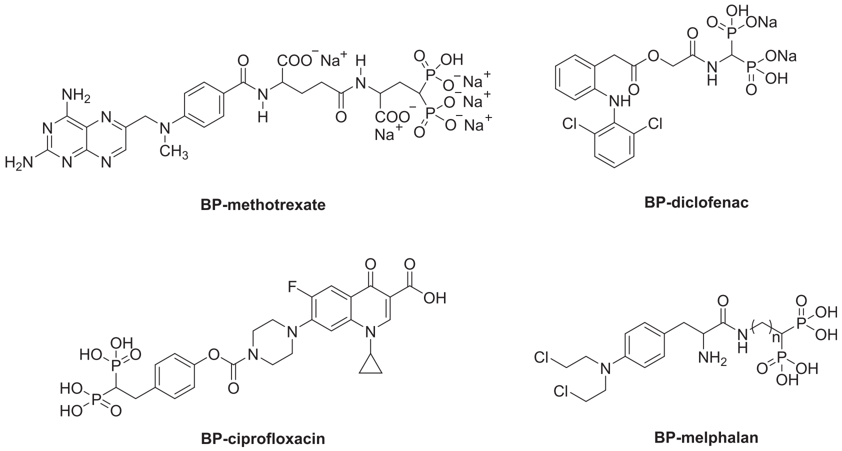
0040-4039/


clodronate etidronate pamidronate alendronate

ibandronate risedronate tiludronate zolendronate

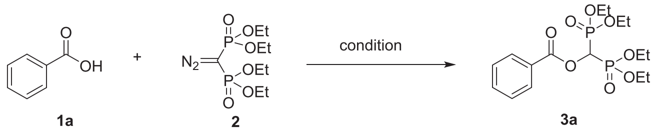
Fig. 1. Structures of clinical bisphosphonate drugs.


BP-methotrexate BP-diclofenac

BP-ciprofloxacin BP-melphalan

Fig. 2. Structures of bone-targeting prodrugs modified with bisphosphonates.

Table 1
Reaction optimization.[a]



1a **2** **3a**

Entry	Catalyst	Solvent	T [°C]	Time	Yield[b]
1	$Cu(OAc)_2$	DCE	80	10 h	65%
2	$Cu(OAc)_2$	DMF	100	24 h	N.R.[c]
3	$Cu(OAc)_2$	CH_3CN	Reflux	24 h	N.R.
4	$Cu(OAc)_2$	DCM	Reflux	24 h	N.R.
5	$Cu(OAc)_2$	Dioxane	100	24 h	N.R.
6	$Cu(OAc)_2$	THF	Reflux	24 h	N.R.
7	$Cu(OAc)_2$	Acetone	Reflux	24 h	10%
8	$Cu(OAc)_2$	Toluene	Reflux	12 h	80%
9	CuI	Toluene	Reflux	18 h	54%
10	$Cu(TFA)_2$	Toluene	Reflux	8 h	85%
11	$Cu(OTf)_2$	Toluene	Reflux	8 h	79%
12	$CuSO_4$	Toluene	Reflux	20 h	60%
13	CuSCN	Toluene	Reflux	20 h	63%
14	CuO	Toluene	Reflux	20 h	69%
15	$Cu(TFA)_2$	Toluene	100	10 h	81%
16	$Cu(TFA)_2$	Toluene	80	15 h	60%
17	$Cu(TFA)_2$	Toluene	60	20 h	55%
18	$Cu(TFA)_2$	Toluene	RT	24 h	N.R.
19[d]	$Cu(TFA)_2$	Toluene	Reflux	8 h	84%
20[e]	$Cu(TFA)_2$	Toluene	Reflux	8 h	80%

[a] Unless noted otherwise, all optimization reactions were performed with **1** (0.41 mmol), **2** (0.61 mmol) and catalyst (20.47 μmol) in solvent (3 mL).

[b] Isolated yields were shown.

[c] N.R.: no reaction.

[d] Increasing **2** to 0.74 mmol.

[e] Increasing **2** to 0.49 mmol.