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Solution-phase parallel tetrahydrofuran synthesis with propargyl alcohols and benzylidene-(or alkylidene-)malonates

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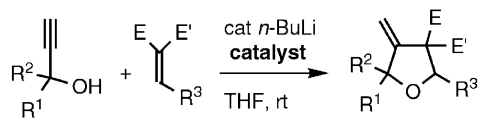
Abstract—A large array of 3-methylene tetrahydrofurans has been synthesized from propargylic alcohols and activated olefins. The reaction is promoted by copper iodide that is removed at the end of the reaction by simple filtration, affording the desired heterocycles in high yield and purity. © 2002 Elsevier Science Ltd. All rights reserved.

The combinatorial synthesis of small ring heterocycles is of great interest for lead discovery in pharmaceutical and agrochemical research.[1] In this area, the ideal goal is to devise reactions which allow to obtain the desired compounds in sufficient pure form without any purification. Our interest in the development of mild and efficient processes for the one-step construction of diverse heterocyclic compounds led us to devise new hetero Michael-initiated cyclisation reactions using readily available, when not purchasable, starting materials.[2–4] For instance, we recently reported the palladium-mediated reaction of propargylic alcohols with activated olefins that offers a convenient access to structurally diverse tetrahydrofuran derivatives (Scheme 1).[2] We later found that copper complexes were even more performing catalysts for such transformations that finally needed only small amounts of copper iodide so as to proceed.[5] We believed that this finding should prove beneficial in devising a practical solution-phase parallel synthesis of tetrahydrofuran libraries because of the low cost of copper iodide and its ease of removal by simple filtration techniques.



R1, R2, R3=aryl, alkyl

E, E'=CO_2Et, CN, COR.

Scheme 1.

For the elaboration of a representative library of 3-methylene tetrahydrofurans (Table 1), we purchased a range of propargylic alcohols (**A**–**G**) and selected a set of Michael acceptors (**1**–**11**) easily accessible by classical Knoevenagel reaction. In our choice, we could take advantage of the vast number of aldehydes, both aromatic and aliphatic that are commercially available. In a typical procedure, a solution of the chosen propargylic alkoxide in THF (0.5 M) prepared by treating the corresponding alcohol (1 mmol) with *n*-BuLi (2.5 N in hexanes, 0.125 mmol) was added to solutions of the different Michael acceptors (0.5 mmol) in THF (0.5 M) using an electronic multipipet. CuI (0.1 mmol)[5] was added after a few seconds to each solution. The resulting mixtures were allowed to react at room temperature for 3 hours and filtered through a short pad of silica (500 mg) using a 12-position SPE vacuum mannifold. The solutions were then simultaneously concentrated using a stream of N_2 with a Techne sample concentrator to recover the final product. As shown in Table 1, the protocol allowed for the preparation of an array of 48 tetrahydrofuran derivatives in good to excellent yields and chemical purities (>90% in most cases) without the need for conventional chromatographic techniques. The low boiling points of the propargylic alcohols employed in the construction of the library ensured easy removal of the excess of reagent. However, if higher boiling point alcohols are needed, the amount of alcohol may be decreased without significant

Keywords: solution-phase synthesis; combinatorial chemistry; copper catalysis; tetrahydrofurans.

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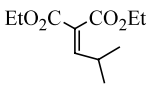
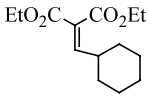
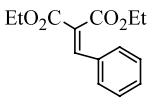
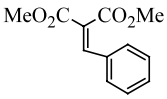
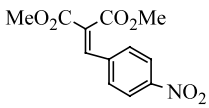
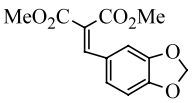
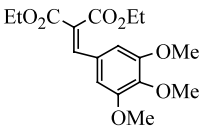
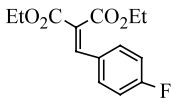
Table 1. Tetrahydrofuran array (yield and purity)[a]

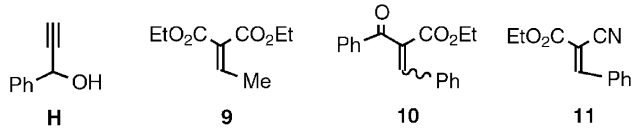
		A	B	C	D	E	F
							
1		100 (95)	100 (95)	100 (>95)	100 (95)	81 (>95)	51 (80)
2		65 (95)	86 (95)	100 (>95)	100 (95)	99 (92)	100 (95)
3		92 (95)	100 (95)	78 (>95)	100 (95)	98 (93)	60 (90)
4		63 (90)	93 (83)	100 (>95)	100 (92)	98 (90)	82 (95)
5		59 (95)	90 (87)	92 (85)	80 (95)	77 (93)	100 (>95)
6		44 (90)	66 (83)	100 (95)	100 (82)	99 (81)	86 (95)
7		76 (95)	64 (90)	66 (>95)	89 (95)	73 (>95)	95 (95)
8		87 (86)	95 (93)	100 (>95)	85 (95)	96 (>95)	100 (95)

[a] For each tetrahydrofuran: the first term indicates the yield based on weight of crude sample; the term in brackets is the percent purity determined by GC–MS analysis. Control NMR analyses have confirmed the structure of the products and the high level of purities observed.

changes in the yields and purities. For instance, equimolecular amounts of 1-phenyl-2-propyn-1-ol (**H**) and **5** were reacted under the standard conditions to give the desired 2,5-diaryltetrahydrofurans in quantitative yield and 90% purity.

It is worth noting that a few exceptions to the general good behaviour of benzylidene (and alkylidene) malonates in this tandem reaction were, nevertheless, observed with the particular Michael acceptors **9**–**11**. Although formation of the expected tetrahydrofurans was always observed, the crude products were often contaminated with substantial amounts of starting materials and/or heterocyclic side products issued from decarboethoxylation or transesterification reactions (Fig. 1).

In summary, our sequential oxa-Michael addition/carbocyclization reaction has been developed into a solution-phase combinatorial protocol for the generation of a representative library of highly substituted tetrahydrofurans in good yield and purity. Owing to the mild reaction conditions and the simple purification procedure, the method appears attractive for the construction of larger libraries, which should include other heteroatom-containing heterocycles.



H **9** **10** **11**

Figure 1.

Acknowledgements

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5. Preliminary experiments showed that the reaction would proceed efficiently with only 5 mol% CuI. However, rapid and total conversion of the Michael acceptors is best achieved by using up to 20 mol% of the copper salt.