ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, **55**, 14976

Received 30th September 2019,
Accepted 20th November 2019

DOI: 10.1039/c9cc07610g

rsc.li/chemcomm

A radical exchange process: synthesis of bicyclo[1.1.1]pentane derivatives of xanthates†

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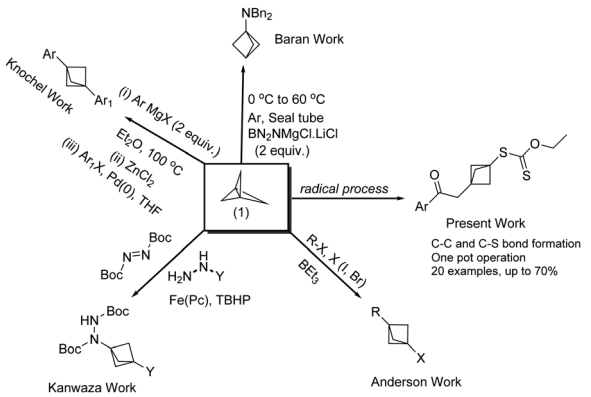
Bicyclo[1.1.1]pentane (BCP) replacement as a bioisostere in drug molecules has an influence on their permeability, aqueous solubility and *in vitro* metabolic stability. Thus, the chemical installation of the BCP unit into a chemical entity remains a significant challenge from a synthetic point of view. Here, we have presented a new approach for the installation of the BCP unit on the xanthate moiety by means of a radical exchange process.

Structure–activity relationships have often facilitated the development of small-ring three dimensional bioisosteres. The bicyclo[1.1.1]pentane (BCP) unit is a unique isosteric replacement for a phenyl ring, with similar geometrical characteristics.[1] Introduction of the BCP moiety into several drug candidates,[2a] such as γ-secretase inhibitors,[2b] mGlu1 receptor antagonists[2c] and LpPLA2 inhibitors,[2d] significantly alters their physicochemical profiles in terms of aqueous solubility, membrane permeability and *in vitro* metabolic stability. Many functionalized BCP derivatives have been obtained by the addition of groups across the reactive central bond of a strained [1.1.1]propellane ring.[3] Considering that the background chemistry has now been well established, and regarding the renewal in interest for such moieties in medicinal chemistry, the scientific community has been recently highly active in finding new methodologies for the introduction of various functional groups on this unique and fascinating hydrocarbon.

Recently, new approaches have been used to gain easy access to BCP containing molecules, as show in Scheme 1. The Baran group solved a long standing problem for the synthesis of amino-BCP derivatives, through a nucleophilic opening of [1.1.1]propellane by using "turbo-amides".[4] Inspired by the pioneer work of de Meijere and coworkers,[3b,5a] Knochel and coworkers developed an elegant and practical method, combining



Scheme 1 BCP unit installation in small molecules.

Grignard reagent-mediated ring-opening of [1.1.1]propellane and Negishi coupling after transmetalation with $ZnCl_2$ to synthesize bis-arylated BCP moieties.[5b] Uchiyama/Kanazawa disclosed an Fe catalyzed multicomponent carboamination of [1.1.1]propellane through a radical approach.[6] Complementary to those studies, the Anderson group also synthesized highly functionalized 1-halo-3-substituted bicyclo[1.1.1]pentanes through atom-transfer radical addition and photoredox catalysis.[7] Recently, the Walsh group suggested a new protocol for the synthesis of BCP benzyl amine derivatives and intercepted anionic intermediates with iodobenzene to evidence the formation of a BCP organolithium intermediate.[8] In addition to this, Brase *et al.* showed a convenient approach for the synthesis of bicyclo[1.1.1]pentyl sulfides through radical chemistry, using various thiols.[9]

A pioneering study by the Zard group on the degenerative radical exchange of thiocarbonylthio derivatives and especially on xanthates was one of the major breakthroughs in the field of radical chemistry. The degenerative radical exchange allows the intermolecular addition of a wide range of xanthate derivatives on unactivated double bonds, with the potential further transformation of the xanthate group.[10] But so far, there has been no precedence of BCP unit installation on a xanthate moiety. In this study, we decided to study the possibility of incorporating

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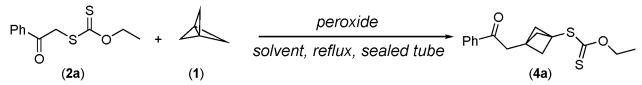
† Electronic supplementary information (ESI) available. CCDC 1911714. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc07610g

Table 1 Screening of reaction conditions[a]



Entry	Propellane (equiv.)	DLP (mol%)	Solvent	Temperature (°C)	Yield (%)
1	1.5	30	DCE	60	32
2	1.5	10	DCE	60	41
3	1.5	10	DCE	80	51
4	1.5	10	DCE	100	51
5	**2.0**	**10**	**DCE**	**80**	**61**
6	2.5	10	DCE	80	61
7	2.0	10	DCM	80	52
8	2.0	10	Toluene	80	46
9	2.0	10	Cyclohexane	80	54
10	2.0	10	Ethyl acetate	80	37

[a] Reaction conditions: xanthate (1.0 equiv.), [1.1.1]propellane (2 equiv.), DLP (0.1 equiv. unless stated substrates), DCE (2.0 M of xanthate after the addition of diethyl solution of [1.1.1]propellane).

xanthate derivatives into a strained ring of [1.1.1]propellane to obtain BCP *O*-ethyl carbonodithioate, using substoichiometric amounts of dilauroyl peroxide (DLP) as a radical initiator. With this inspiration in mind, our initial investigation began by treating model xanthate **2a** (1 equiv.) with [1.1.1]propellane (0.6–0.8 M in Et_2O, 1.5 equiv.) and DLP (0.3 equiv.) at 60 °C in dichloroethane (DCE) in a sealed tube. To our delight, the BCP unit (**4a**) was isolated in 32% yield (entry 1, Table 1) along with some undesired product (competitive opening of propellane by decyl radicals). To the best of our knowledge, the product is the first of its kind, a BCP unit with a ketone moiety and a xanthate group, which can further modified to more useful products.[11] Another appealing side to this methodology resides in the ability to form C–C and C–S bonds across the reactive central bond of the strained [1.1.1]propellane ring, without using a metal catalyst. Encouraged by this first result, other reaction parameters such as the quantity of [1.1.1]propellane, the amount of radical initiator, temperature and solvents were studied, to achieve the highest yield. To control the formation of the undesired product, the loading of DLP was decreased from 0.3 equiv. to 0.1 equiv., resulting in an improved yield of 41% (entry 2, Table 1). To further improve the yield, the temperature was increased from 60 °C to 80 °C to optimize the fragmentation of the radical initiator (entry 3, Table 1).

A further increase in temperature from 80 °C to 100 °C did not have any effect on the yield (entry 4, Table 1). Next, we moved to the quantity of [1.1.1]propellane (0.6–0.8 M in Et_2O). Increasing the quantity from 1.5 equiv. to 2.0 equiv. gave a good yield of 61% (entry 5, Table 1). Increasing the quantity further to 2.5 equiv. of (**1**) did not alter the yield of the reaction (entry 6, Table 1). Screening of other solvents showed that DCM (52%), toluene (46%), cyclohexane (54%), and ethyl acetate (37%) were less productive than DCE (entries 7–10, Table 1).

Finally, it was found that the ideal conditions for this transformation were DLP (10 mol% for aromatic substrates and 20 mol% for aliphatic substrates), [1.1.1]propellane to 2.0 equiv. in DCE at 80 °C in a sealed tube (entry 5, Table 1). Furthermore, the structure of the BCP unit (**4a**) was confirmed by X-ray crystallography, Fig. 1.

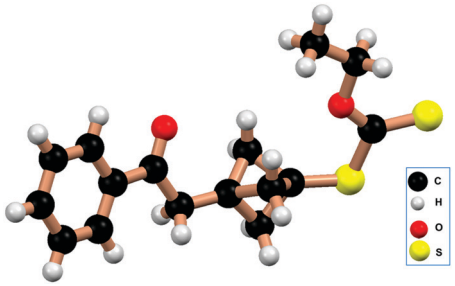
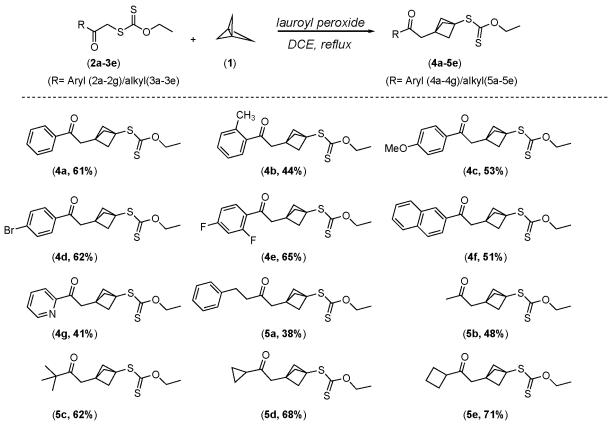


Fig. 1 Crystal structure of **4a**.

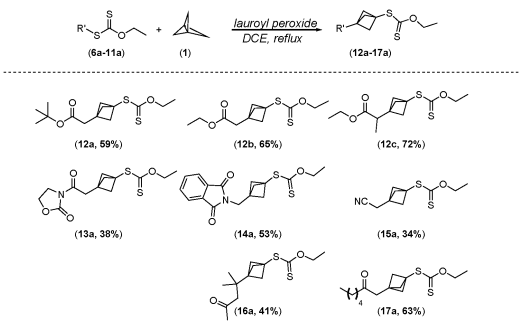
After achieving the optimized conditions, this methodology was applied to xanthates with various aryl and alkyl ketones on the backbones of the xanthates (Schemes 2 and 3). At first, the effects of substituents on the aryl ring of xanthates were examined. The electron-donating aryl substituted (*viz.* *o*-Me (**2b**) and *p*-OMe (**2c**)) xanthates reacted with (**1**) under optimized conditions, and we successfully obtained the desired BCP products (**4b** and **4c**) in average yields of 44 and 53%, respectively. However, when the aryl ring contained electron-withdrawing groups such as *p*-Br (**2d**) and di-F (**2e**), the reactions proceeded slightly better, to give their corresponding BCP products **4d** and **4e** in 62% and 65% yields, as shown in Scheme 2.

A BCP moiety containing pyridine group (**4g**) was successfully prepared by the reaction of [1.1.1]propellane (**1**) with xanthate (**2g**), in a moderate yield. Moving from aryl to alkyl xanthates, to see the influence on reactivity, we then checked various groups such as acetyl (**3b**), *t*-butyl (**3c**), cyclopropyl (**3d**) and cyclobutyl (**3e**) in the current protocol. Average to good yields up to 71% were obtained in those cases with good reproducibility.

We then decided to check the variety of xanthate structures with different functional groups in order to diversify the portfolio of available structures, as depicted in Scheme 3. First, the scope was extended to the case of ester and substituted esters such as *tert*-butyl ester (**6a**), ethyl ester (**6b**) and α-methyl



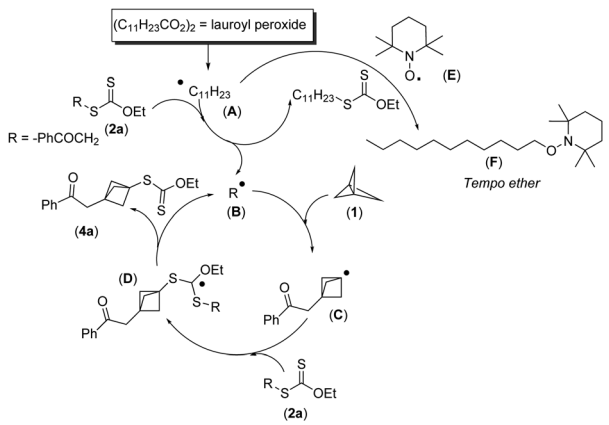
Scheme 2 Scope of BCP moiety installation with xanthates **2a–3e**. Reaction conditions: xanthate (1.0 equiv.), [1.1.1]propellane (2 equiv.), DLP (0.1 equiv., for aromatic ketones **2a–2g** and 0.2 equiv. for aliphatic ketones **3a–3e**), DCE (2.0 M of xanthate after the addition of diethyl solution of [1.1.1]propellane) at 80 °C. Isolated yields.



Scheme 3 Scope of BCP moiety installation with xanthates **6a–11a**. Reaction conditions: xanthate (1.0 equiv.), [1.1.1]propellane (2.0 equiv.), DLP (0.2 equiv.), DCE (2.0 M of xanthate after the addition of diethyl solution of [1.1.1]propellane) at 80 °C. Isolated yields.

ester (**6c**). All the esters yielded their corresponding products in satisfactory yields (69–72%). The reaction was also successful with an acyloxazolidinone, yielding the corresponding adduct (**13a**) in a more moderate 38% yield. We also aimed to demonstrate that other functional groups could be introduced by this method. Interestingly, xanthate **8a**, previously described by Zard *et al.* for radical aminomethylation of alkenes,[12] worked well under our optimized conditions and gave the desired product in a decent 53% yield. The unusual substrate **10a** in which the xanthate group is one carbon away from the ketone gave the desired product (**16a**) in a moderate yield, suggesting the formation of a stable radical at the tertiary carbon centre.[13] Thus, this particular experiment suggested that the current methodology is not restricted to a specific xanthate moiety and has good potential regarding its scope.

Based on literature reports and mechanistic investigations,[7,10b,14] a plausible mechanism for this transformation is depicted in Scheme 4. A radical (**B**) is first formed by the reaction of the xanthate with the decyl radical arising from the fragmentation/decarboxylation of DLP. The alkyl radical (**B**) reacts then with **1** to give the radical intermediate **C**.[10a] The reaction of **2a** with radical **C** gives rise the stabilized intermediate radical **D**. Finally, radical cleavage of intermediate **D** gives the BCP product **4a**. To gain further insight into the mechanism, a



Scheme 4 Proposed mechanism for the formation of BCP.

reaction was performed in the presence of TEMPO (**E**) to capture the proposed intermediate in the catalytic cycle. Unfortunately, we were not able to isolate any of the trapped intermediates, but we were able to observe the formation TEMPO ether of the decyl radical (**F**), along with the starting material.

In conclusion, we have developed an efficient method for the synthesis of functionalized BCP derivatives with xanthate moieties by means of a radical exchange process. This reaction uses simple conditions and one-pot operations and tolerates different functional groups present in the xanthate moiety. Thus, it opens up a new avenue for medicinal chemistry. Work is now in progress for studying the transformation of the xanthate group for further transformations and implementing these new scaffolds.

We gratefully acknowledge financial support from the Université Catholique de Louvain (UCL), FNRS (FRIA grant to G. Marghem), FRS-FNRS (Chargé de recherches – CR, post-doctoral grant to S. Rout) and the Chinese Scholarship Council (PhD grant to J. Lan).

Conflicts of interest

There are no conflicts to declare.

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