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Substitution of chlorocyclobutanones with xanthate salts. The remarkable effect of added base

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This Letter is dedicated with respect to the memory of our friend, Dr. Christian Marazano

ABSTRACT

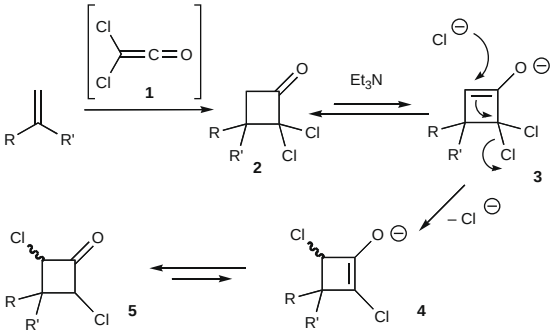
The substitution reaction of chlorocyclobutanones with dithiocarbonates (xanthates) is greatly accelerated by the addition of a mild base such as DABCO or DBU.

As part of our ongoing work on the chemistry of xanthates (dithiocarbonates),[1] we required a convenient access to α-xanthyl cyclobutanones. These could not normally be obtained from α-chlorocyclobutanones by the nucleophilic substitution of the chloride, and a circuitous route via the more reactive bromide had to be used.[2] Even then, the substitution was sometimes capricious, giving unexpected ring-expanded products and forcing us to replace the usual *O*-ethyl xanthate with the more robust *O*-neopentyl xanthate. We have now found that by addition of an organic base, the substitution process is accelerated considerably, allowing us to start with the more readily accessible α-chlorocyclobutanones and to access derivatives which would be extremely difficult to obtain otherwise.

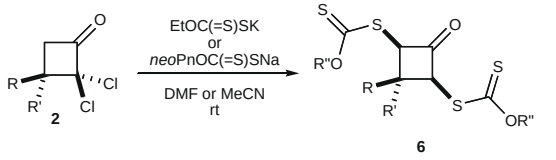
α,α-Dichlorocyclobutanones such as **2** can be produced by cycloaddition of in situ generated dichloroketene **1** with various electron-rich alkenes or dienes.[3] They undergo a number of unusual transformations, but the triethylamine induced *cine* isomerisation into the corresponding α,α′-dichlorocyclobutanones **5** was especially intriguing (Scheme 1).[4] Only scant mechanistic studies for this transformation are available, but the ionic chain process displayed in Scheme 1 and involving S_N2' substitution on enolate **3** appears reasonable (vide infra). We therefore contemplated the possibility of replacing the triethylamine with a xanthate salt, which would act both as a mild base and as a nucleophile.[5,6]

Indeed, treatment of dichlorocyclobutanone **2a** with potassium *O*-ethyl xanthate or sodium *O*-neopentyl xanthate in acetonitrile resulted in the smooth formation of rearranged dixanthates **6a$_1$** and **6a$_2$** in 84% and 73% yields, respectively, presumably through further reaction of an intermediate α-chloro-α′-xanthate (Scheme 2; *neo*Pn = neopentyl).

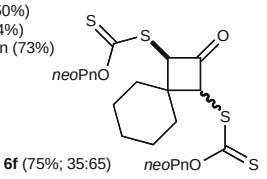
In the same way, except for the use of DMF as the reaction solvent, dixanthates **6b–f** were obtained from the corresponding



Scheme 1. *Cine* rearrangement of α,α-dichlorocyclobutanones.



6a$_1$, R = H, R' = 3-butenyl, R" = Et (84%)
6a$_2$, R = H, R' = 3-butenyl, R" = neoPn (50%)
6b$_1$, R = H, R' = 4-t-BuC6H4-, R" = Et (84%)
6b$_2$, R = H, R' = 4-t-BuC6H4-, R" = neoPn (73%)
6c, R = R' = Et, R" = neoPn (71%)
6d, R = R' = Ph, R" = neoPn (80%)
6e, R = Me, R' = Ph, R" = neoPn (81%)



6f (75%; 35:65)

Scheme 2. Synthesis of α,α′-bis(xanthyl)-cyclobutanones.

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dichlorocyclobutanones **2b–f** (same definition for substituents R and R' for **2a–f** and **6a–f**). We found DMF to be a generally better solvent than acetonitrile, and the use of the neopentyl group simplified the interpretation of the NMR spectra.

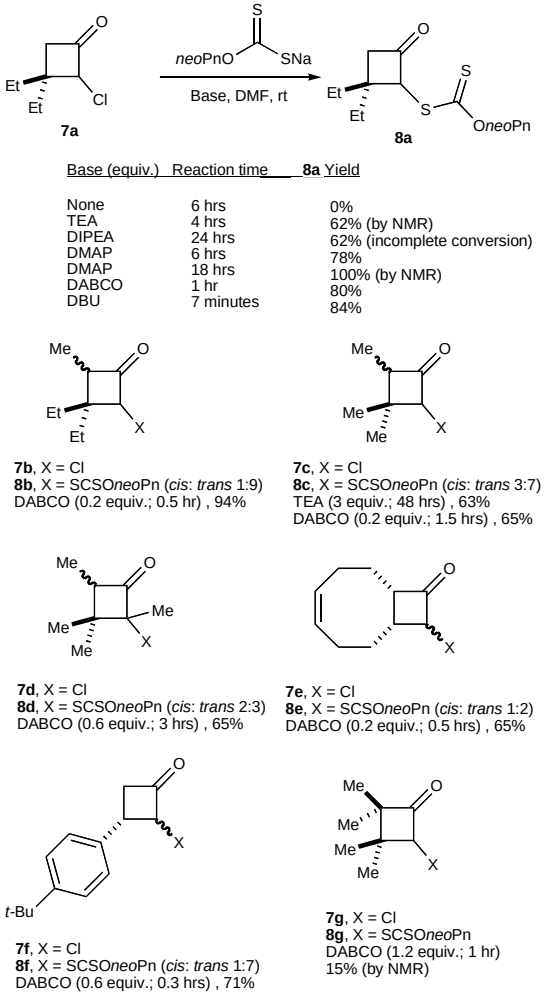
The replacement of both chlorines in α,α-dichlorocyclobutanones by a nucleophile does not seem to have been reported, and the present reaction provides a convenient access to useful dixanthates. Surprisingly, however, the smooth reaction of the dichlorocyclobutanones contrasted sharply with the total lack of reactivity of the monochlorocyclobutanones towards substitution by the xanthate.[7] We conjectured that, in the case of the less acidic monochlorocyclobutanones, the xantate salt was perhaps too weak a base to induce the formation of useful concentrations of the corresponding enolates. Using 2-chloro-3,3-diethyl-cyclobutanone **7a** as a test substrate, we repeated the substitution in the presence of added base. Indeed, incorporation of 1.7 equiv of triethylamine resulted in a reasonably smooth reaction to give 62% (by NMR) of the desired xanthate **8a** (Scheme 3).

Diisopropylethylamine (DIPEA) was less effective, presumably because of steric hindrance. To obtain the same yield, 6 equiv of the base and a 24 h reaction time were required. In contrast, DMAP and especially DABCO and DBU proved significantly more efficient: with only 0.2 equiv of the DABCO or DBU, an essentially complete conversion was observed after 1 hour for the former and 7 min for the latter, the isolated yield of **8a** being 80% and 84%, respectively.

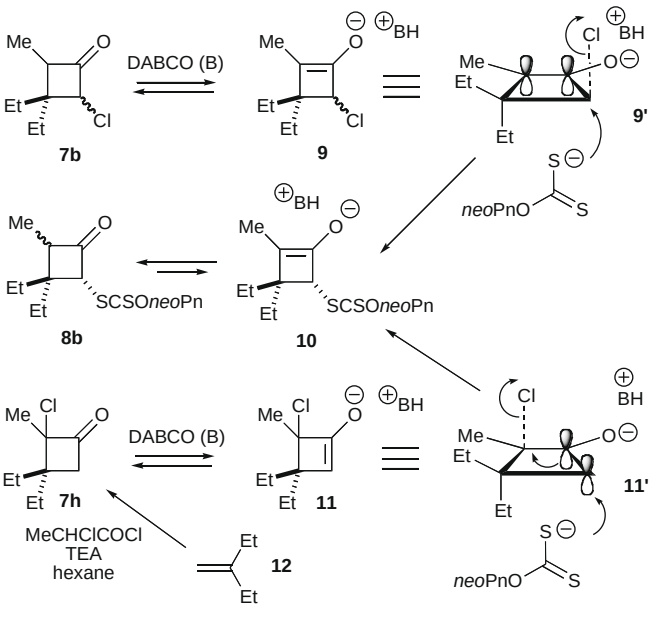
Even though addition of DBU resulted in the fastest reaction, subsequent experiments were conducted in the presence of the weaker base, DABCO, as it was easier to monitor the consumption of the starting chloride and avoid the formation of side products due to overexposure to the base. As depicted in the lower half of Scheme 3, treatment of chlorides **7b–f** with sodium *O-neo*pentyl xanthate in DMF in the presence of substoichiometric amounts of DABCO gave rise to the corresponding xanthates **8b–f** in good yield and short-reaction times. Again, no substitution was observed in the *absence* of DABCO. It is worth pointing out that the chlorine in **7a–g** is *neo*pentylic and, in the case of **7d**, also tertiary, and therefore almost impossible to displace in normal circumstances. That it can be smoothly substituted under such mild conditions is thus quite remarkable. 2-Chloro-3,3,4,4-tetramethyl cyclobutanone, **7g**, which cannot produce the desired enolate (vide infra), reacted sluggishly to give xanthate **8g** in the presence of DABCO, and not at all in its absence.

Various hypotheses can be cast to rationalize the extreme ease of substitution of the chlorine atom in the presence of added base, but we believe the most coherent to be the one detailed in Scheme 4 for the case of **7b**. The geometry of the corresponding enolate **9** allows an efficient overlap between the high lying filled π orbital (HOMO of the enolate) with the empty σ* of the C–Cl bond (better seen in **9'**). The energy level of the HOMO of the enolate is, in addition, increased by the ring strain inherent in cyclobutenes,[8] bringing it closer to the level of the σ* and further improving the extent of the interaction. By partially populating the antibonding molecular orbital, this interaction causes a significant weakening, and hence lengthening, of the C–Cl bond. This stereoelectronic configuration is qualitatively similar to that prevailing at the anomeric position in carbohydrates, where one of the lone pairs of the ring oxygen is ideally disposed to interact with the σ* of the axial anomeric C–X bond causing its lengthening and increased reactivity towards substitution (the 'anomeric effect').

The substitution reaction by the xanthate salt on enolate **9** takes place by an S_N2 fashion to give ultimately compound **8b** in high yield following the protonation of enolate **10**. The regioisomeric chloride, **7h**, easily prepared by reaction of in situ generated methylchloroketene with 2-ethyl-butene **12**, leads to enolate **11**, where the S_N2 reaction mode is hampered by the methyl group. The substitution now takes place in an S_N2' fashion (shown on **11'**) to give xanthate **8b** in 52% overall yield from alkene **12**, via same enolate **10**. Thus, the reaction leads to identical products starting from



Scheme 3. Effect of added base.



Scheme 4. Mechanistic rationale for the effect of base.

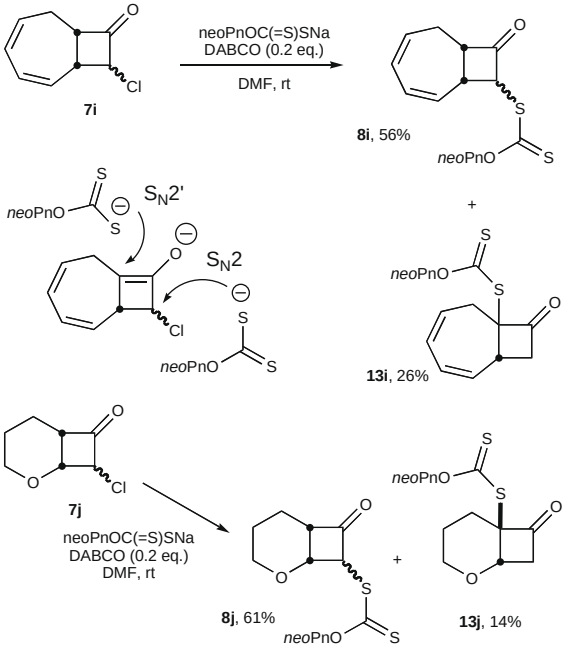
either chlorides **7b** or **7h**. In the case of **7g**, the required enolate cannot be formed, and the small yield of product probably arises by an alternative route involving a carbene, generated by α-elimination of the chloride.

In the case of slightly strained, fused cyclobutanones, the reaction furnished two regioisomeric products, in contrast to the preceding examples. Thus, reaction of chlorocyclobutanone **7i** under the usual conditions furnished, in addition to the expected xanthate **8i**, a significant amount of regioisomer **13i**. Clearly, the S_N2 and S_N2' occur with comparable rates (Scheme 5). A similar behaviour was exhibited by dihydropyrane fused chlorocyclobutanone **7j**, which afforded **8j** and **13j** in 61% and 14% yields, respectively.

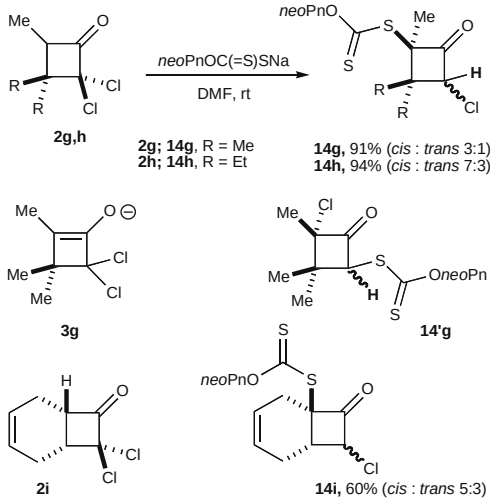
In further support of the postulated mechanism, we found that it is possible to obtain *mono*-xanthates from dichlorocyclobutanones by blocking the enolisation after the introduction of the first xanthate group and therefore preventing the second substitution from taking place, as illustrated by the examples displayed in Scheme 6.

Treatment of **2g** with sodium *O-neo*pentyl xanthate in DMF gave a high yield of distal chloroxanthate **14g**, arising by an S_N2' reaction on the corresponding enolate **3g**. Clearly, further enolisation in **14g**, in a manner allowing substitution of the second chlorine is no longer possible and only the mono-xanthate is obtained. Furthermore, none of the isomeric products **14′g**, possibly derived from a prior cine-rearrangement of the starting geminal dichloride **2g** followed by S_N2 substitution by the xanthate salt, was observed.[9] In the same manner, dichloroketones **2h** and **2i** furnished xanthates **14h** and **14i** in 94% and 60% yield, respectively. No added base is required in these cases, in line with the greater acidity of the dichlorocyclobutanones, as discussed above (Schemes 1 and 2).

In summary, this study has provided a simple solution to the synthesis of α-xanthyl-cyclobutanones,[10] which can now be further processed through the powerful xanthate transfer technology.[1] Extension of this approach to other α-chloroketones is currently being investigated. Preliminary results with α-chlorocyclopentanones and α-chlorocyclohexanones seem to indicate a much less pronounced effect of added base. It must be pointed out, however, that in these derivatives the direct substitution of the chloride by a normal S_N2 process is already reasonably efficient.



Scheme 5. Cases leading to regioisomers.



Scheme 6. Synthesis of mono-xanthates from α,α-dichlorocyclobutanones.

Acknowledgement

We thank Ecole Polytechnique for generous financial support to one of us (R.H.).

Supplementary data

Experimental procedures, characterization data and copies of ^1H, ^{13}C and NMR spectra are presented. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.133.

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8. The ionization potential of cyclobutene is 9.59 eV, while that of ethylene is 10.51 eV. See: Wiberg, K. B.; Ellison, C. B.; Wendoloski, J. J.; Brundle, C. R.; Kuebler, N. A. *J. Am. Chem. Soc.* **1976**, *98*, 7179.
9. The spectroscopic distinction between isomers **14g** and **14′g** is not obvious. To resolve this ambiguity, the xanthate was subjected to ozonolysis, which cleanly converted the thiocarbonyl group into a carbonyl (Quiclet-Sire and Zard, S. Z., unpublished work). In the case of **14′g**, this should have caused a significant shift (ca 0.5 ppm) in the ^{1}H NMR signal of the ring proton (indicated in bold type), which was not observed.
10. *Typical experimental procedure*: To a stirred solution of 2-chlorocyclobutanones **2** (1.0 mmol) in DMF (1 mL) under nitrogen, were added sodium *O*-neopentyl xanthate (279 mg, 1.5 mmol), and DABCO (24 mg, 0.20 mmol). Stirring was continued until reaction was complete (TLC). Brine and diethyl ether were then added, and the aqueous layer was extracted twice with diethyl ether. The organic layer was then washed repeatedly with water then with saturated ammonium chloride, dried over anhydrous $MgSO_4$, and the solvent removed in vacuo. In most cases, the crude residue was essentially pure α-xanthylcyclobutanone **8**; otherwise, it was further purified by chromatography.