Pergamon

Tetrahedron Letters, Vol. 38, No. 39, pp. 6901-6904, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01590-6

Cyclization of 1-(Carbamoyl)dichloromethyl Radicals upon Activated Alkenes. A New Entry to 2-Azabicyclo[3.3.1]nonanes

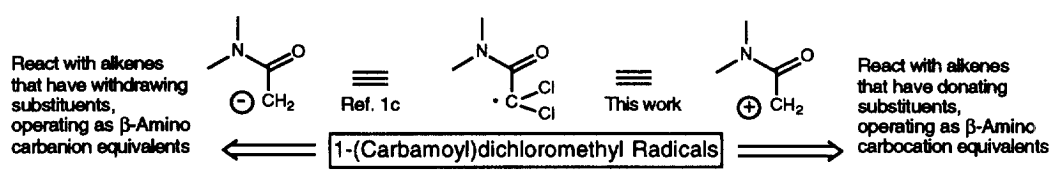
Josefina Quirante, Carmen Escolano, Laura Costejà, and Josep Bonjoch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

Abstract: The synthesis of 2-azabicyclo[3.3.1]nonanes using a radical cyclization process as the piperidine ring-forming step is described. The reaction involves 1-(carbamoyl)-dichloromethyl radicals which react intramolecularly with simple or activated alkenes, such as enol acetates or silyl enol ethers. © 1997 Elsevier Science Ltd.

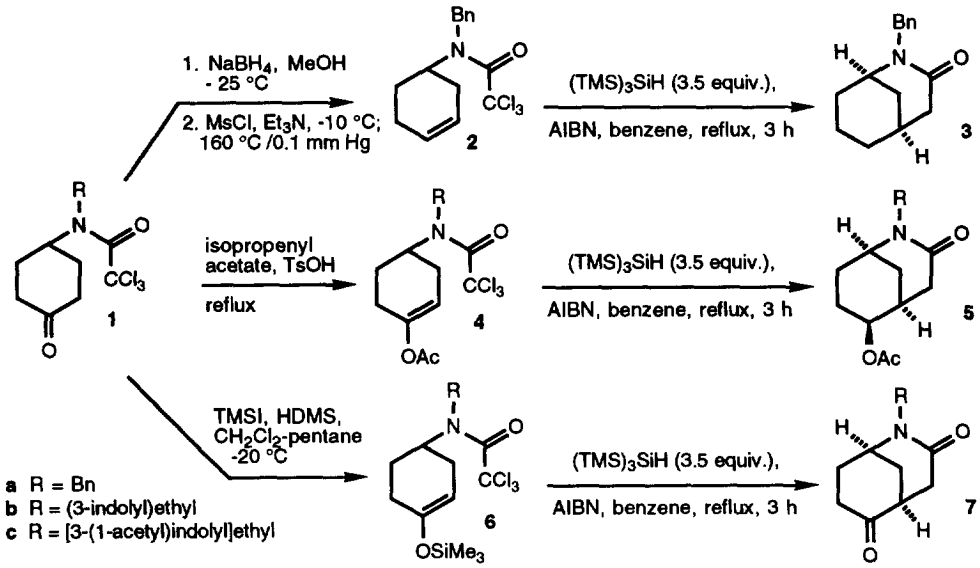
1-(Carbamoyl)dichloromethyl radicals, generated by homolysis of the corresponding trichloroacetamides, using either hydride reagents or metals (Cu, Ru, Ni), are promising reactive intermediates which have been used for the synthesis of β-, γ-, and δ-lactam ring systems.[1-3] Despite the electrophilic character of this radical type, non-activated alkenes or alkenes with an electron-withdrawing substituent act as radical acceptors in all processes described so far.[2e] In previous studies,[1b,c] we have described the radical cyclization of 1-(carbamoyl)dichloromethyl radicals upon alkenes bearing an electron-withdrawing substituent (CN or CO_2Me) to elaborate the piperidine ring of a 2-azabicyclo[3.3.1]nonane nucleus, which has allowed the total synthesis of the heteroyohimban alkaloid Melinonine E.[1b]

In this communication we describe the usefulness of 1-(carbamoyl)dichloromethyl radicals in promoting 6-*exo* cyclizations upon activated alkenes such as enol acetates or silyl enol ethers[4] as well as non-activated alkenes, exemplified by the synthesis of several 2-azabicyclo[3.3.1]nonanes.[5] It seems, according to these and earlier results, that the 1-(carbamoyl)dicloromethyl radical has, as can be expected,[6] an ambiphilic character. It acts as a nucleophilic species with electron-poor alkenes, behaving as an equivalent of a β-aminocarbanion, while, on the other hand, it can also act as an electrophilic species with electron-rich alkenes, its behaviour being the equivalent of a β-aminocarbocation (synthon with inverted polarity) (Scheme 1).[7]



Scheme 1

E-mail: bonjoch@farmacia.far.ub.es



Scheme 2

We first examined the behaviour of *N*-cyclohexenyltrichloroacetamide **2**, prepared from cyclohexanone **1a** by means of reduction and dehydration in a 64% overall yield (Scheme 2).[8-10] When a solution of **2** in benzene was treated with $(TMS)_3SiH$ and AIBN at reflux temperature, after work-up and chromatography, azabicyclic lactam **3** was isolated in 66% yield.[11] In a similar manner, treatment of enol acetate **4a** with $(TMS)_3SiH$-AIBN under identical reaction conditions, provided morphan **5a**, as a single diastereoisomer, with the same yield.[12] Enol acetate **4a** was obtained by treatment of cyclohexanone **1a** with TsOH and isopropenyl acetate (62% yield).

From trimethylsilyl enol ether **6a**, using the typical experimental procedure with $(TMS)_3SiH$-AIBN, bicyclic dione **7a** was obtained in one step (69% yield).[13] The radical precursor **6a** was prepared in 86% yield from cyclohexanone **1a** by treatment with trimethylsilyl iodide and hexamethyldisilazane.[14] The formation of 2-azabicyclo[3.3.1]nonane-3,6-dione **7a** directly from **6a** is noteworthy, since it constitutes an example of a new synthetic method for the preparation of 1,4-dicarbonyl compounds (i.e. γ-ketoamides). We suggest that the ketone carbonyl group comes from the radical centered at C-6, arising from the cyclization process, which may capture a chlorine radical from the dichloroacetamide intermediate followed by evolution of the generated α-chloro silylether.[15,16]

In order to explore the scope of this cyclization-type in the preparation of more complex compounds (*ca* indole alkaloids), we examined the behaviour of the trichloroacetamides **4c** and **6b** which incorporate a tryptamine unit. These radical precursors were obtained from **1b**[1b] following the foregoing reactions used for the **a** series. Under the reaction conditions used for the formation of enol acetate from indole ketone **1b**, acetylation upon NH-indole also took place, giving the acetylated indole derivative **4c** (Scheme 2). After radical cyclization and the subsequent reductive process, using the same reaction conditions as described above for the *N*-benzyl series, azabicyclic systems **5c** (60%) and **7b** (58%) were isolated.

The relative configuration at C-6 in compounds **5a** and **5c** (equatorial acetoxy group) was deduced

from the multiplicity (qd, J = 13.5 and 3.5 Hz) of H-7_{ax} (assigned from 2D NMR spectra), which indicates the axial disposition for the group at C-6. Additionally, the ^{13}C NMR data (Table 1) are in agreement with this assignment. The preferred formation of these estereoisomers indicates that the hydrogen atom transfer from the hydride reagent to the α-acetoxy radical intermediate occurs in an axial fashion, the kinetic mode for such processes in cyclohexyl radicals.[17]

Table 1. ^{13}C NMR Chemical Shifts (δ) of 2-Azabicyclo[3.3.1]nonanes[a]

Comp	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	CH_2Ph[b]	Other
3	51.2	171.4	37.7	27.0	31.9	16.6	28.2	32.1	48.0	
5a	49.9	170.3	31.5	31.3	73.3	22.3	27.6	30.8	48.1	21.2, 170.4
5c	51.9	170.3	31.6	31.1	73.2	22.1	28.2	30.6		23.4, 46.5[c,d]
7a	50.0	168.3	35.0	44.2	210.7	34.0	29.9	32.3	48.4	
7b	52.0	168.1	35.1	44.1	211.1	33.9	30.4	31.9		23.6, 47.8[c]

[a] In $CDCl_3$ (75.5 MHz). Values assigned on the basis of HMQC spectra. [b] Phenyl ring carbons were found at 127.4 (± 0.3) 127.8 (± 0.1), 128.6 (± 0.2), 137.4 (± 0.3) for **3**, **5a** and **7a**. [c] Indole ring carbons were found at 116.6, 118.8, 119.7, 122.5, 123.5, 125.3, 130.3, 135.7 for **5c** and at 111.2, 113.0, 118.7, 119.4, 121.9, 122.1, 127.4, 136.2 for **7b**. [d] OAc (21.2, 170.4); NAc (24.0, 168.3).

In summary, we have evaluated the reactivity of 1-(carbamoyl)dichloromethyl radicals with unsubstituted alkenes and alkenes bearing an electron-donating group (OAc, $OSiMe_3$). We have found that these radicals are able to cyclize upon unsubstituted and electron-rich alkenes, giving the corresponding azabicyclo derivatives, with the same effectiveness as upon electron-poor acceptors, which we observed in previous studies.[1c]

Acknowledgments. Support for this research was provided by DGICYT (Spain) through Grant PB94-0858. Thanks are also due to the 'Comissionat per a Universitats i Recerca' (Generalitat de Catalunya) for Grant SGR95-00045 and a fellowship to C.E.

REFERENCES AND NOTES

1. For the synthesis of six-membered rings from trichloroacetamides, see: (a) Hirai, Y.; Hagiwara, A.; Terada, T.; Yamazaki, T. *Chem. Lett.* **1987**, 2417-2418. (b) Quirante, J.; Escolano, C.; Bosch, J.; Bonjoch, J. *J. Chem. Soc., Chem. Commun.* **1995**, 2141-2142. (c) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391-1402.
2. For the synthesis of five-membered rings from trichloroacetamides, see: (a) Nagashima, H.; Wakamatsu, N.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682-1689. (b) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464-470. (c) Ishibashi, H.; Kameoka, C.; Iryama, H.; Kodama, K.; Sato, T.; Ikeda, M. *J. Org. Chem.* **1995**, *60*, 1276-1284. (d) Parsons, A.F. *Tetrahedron* **1996**, *52*, 6739-6758. (e) For a related process, in which a cyclization of a trichloroacetamide occurs upon a phenol ring, using Ni as a promoter, see: Bovin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 9553-9556.
3. For the synthesis of four-membered rings from trichloroacetamides, see: Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1397-1400.
4. To our knowledge this type of cyclization has not been precedented. Alkyl radicals usually do not react

with silyl enol ethers: Urabe, H.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 1355-1358. For the use of (ethoxymethoxy)alkenes as radical acceptors, see: Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802-4809.

5. The 2-azabicyclo[3.3.1]nonane framework constitutes a structural subunit of many types of alkaloids. Methods inducing the ring closure of this heterocyclic system are of great interest for the development of synthetic approaches to natural products which embody this nucleus.
6. It is known that electrophilic radicals have an ambiphilic behaviour with alkenes: Curran, D. P.; Eichenberger, E.; Collis, M.; Roepel, M. G.; Thoma, G. *J. Am. Chem. Soc.* **1994**, *116*, 4279-4288.
7. For retrosynthetic planning using radical reactions, see: Curran, D. P. *Synlett* **1991**, 63-72.
8. All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accordance with its infrarred, 500 MHz ^{1}H NMR, and 75.5 MHz ^{13}C NMR spectra, as well as appropiate parent ion identification by HRMS. In addition, compounds **1a**, **1b**, **4c**, **5a** **5c**, **6a**, **6b**, and **7b** gave satisfactory combustion analysis.
9. Trichloroacetamide **1a** was prepared from 4-benzylaminocyclohexanone ethylene acetal[10] by acetylation (Cl_3COCl, pyridine, CH_2Cl_2, rt, 80% yield) followed by hydrolysis of the acetal moiety (3 N HCl, THF, rfx, 71%).
10. (a) Johnson, S.J. *J.Org. Chem.* **1995**, *60*, 8089-8092. (b) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 196-197.
11. **General Experimental Procedure**: To a boiling solution of **2** (518 mg, 1.56 mmol) and AIBN (271 mg, 1.65 mmol) in anhydrous benzene (13 ml) was added $(TMS)_3SiH$ (1.68 ml, 5.46 mmol) dropwise, and the mixture was heated under reflux for 3 h. After the solvent had been evaporated off, the residue was chromatographed (3% MeOH in CH_2Cl_2) to give **1-benzyl-2-azabicyclo[3.3.1]nonan-3-one** (**3**, 237 mg, 66%) as a yellow oil: IR (NaCl) 1637; ^{1}H NMR ($CDCl_3$, COSY) 1.34 (ddd, J = 13.5, 8.5, 2, 1 H, H-8_{ax}), 1.48-1.54 (m, 2 H, H-7), 1.58 (m, 1 H, H-6_{ax}), 1.64 (masked dm, 1 H, H-6_{eq}), 1.67 (ddd, J = 13, 5, 3, 1 H, H-9_{anti}), 1.76 (dm, J = 13, 1 H, H-8_{eq}), 1.79 (dm, J = 13, 1 H, H-9_{syn}), 2.21 (m, $W_{1/2}$ = 15, 1 H, H-5_{eq}), 2.34 (dt, J = 18.5, 1, 1 H, H-4eq), 2.71 (dd, J = 18.5, 7, 1 H, H-4_{ax}), 3.44 (m, $W_{1/2}$ = 9, 1 H, H-1_{eq}), 3.85 and 5.30 (2 d, J = 15, 2 H, CH_2Ph), 7.21-7.31 (m, 5 H, ArH).
12. **(1*RS*,5*SR*,6*SR*)-6-Acetoxy-1-benzyl-2-azabicyclo[3.3.1]nonan-3-one (5a)**: IR (NaCl) 1731, 1639; ^{1}H NMR ($CDCl_3$, COSY) 1.46 (tdd, J = 13, 3.5, 2, 1 H, H-8_{ax}), 1.53 (qd, J = 13.5, 4.5, 1 H, H-7_{ax}), 1.74 (ddd, J = 13.5, 5, 3, 1 H, H-9_{anti}), 1.83 (dm, J = 12, 1 H, H-7_{eq}), 1.86 (dm, J = 12, 1 H, H-8_{eq}), 1.95 (ddd, J = 13.5, 7, 3.5, 1 H, H-9_{syn}), 2.05 (s, 3 H, CH_3), 2.39 (m, $W_{1/2}$ = 13, 1 H, H-5_{eq}), 2.54 (dd, J = 18.5, 7, 1 H, H-4_{ax}), 2.75 (dt, J = 19, 1, 1 H, H-4_{eq}), 3.44 (br s, 1 H, H-1_{eq}), 4.85 (dt, J = 11, 4.5, 1 H, H-6_{ax}), 3.93 and 5.26 (2 d, J = 15, 2 H, CH_2Ph), 7.24-7.34 (m, 5 H, ArH).
13. **1-Benzyl-2-azabicyclo[3.3.1]nonan-3,6-dione (7a)**: IR (NaCl) 1713, 1641; ^{1}H NMR ($CDCl_3$, COSY) 1.71 (tdd, J = 13.5, 5.5, 2.5, 1 H, H-8_{ax}), 1.99 (dm, J = 13.5, 1 H, H-9_{anti}), 2.06 (ddd, J = 13, 6, 3, 1 H, H-9_{syn}), 2.13 (m, 1 H, H-8_{eq}), 2.28 (dm, J = 15.5, 1 H, H-7_{eq}), 2.41 (ddd, J = 16, 13, 7, 1 H, H-7_{ax}), 2.47 (dd, J = 17, 1.5, 1 H, H-4_{eq}), 2.74 (dd, J = 17, 7.5, 1 H, H-4_{ax}), 2.76 (m, 1 H, H-5_{eq}), 3.59 (m, 1 H, H-1_{eq}), 4.03 and 5.25 (2 d, J = 15, 2 H, CH_2Ph), 7.20-7.30 (m, 5 H, ArH).
14. Miller, R. D.; Mckean, D. R. *Synthesis* **1979**, 730-732.
15 For a related process, see: Giese, B.; Horler, H.; Leising, M. *Chem. Ber.* **1986**, *119*, 444-452.
16. For formation of 1,4-dicarbonyl compounds by reaction of 1-carbamoyl radicals, generated by oxidation of an α-tributylstannyl amide with Ce^{IV} compounds, upon silyl enol ethers, see: Kohno, Y.; Narasaka, K. *Chem. Lett.* **1993**, 1689-1692.
17. Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067-4079.

(*Received in UK* 3 *July* 1997; *accepted* 1 *August* 1997)