Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 23 Sep 2006.

To cite this article: I. Lachaise, K. Nohair, M. Hakiki & J. Y. Nédélec (1995): A Straightforward Synthesis of [3.3.0]Bicyclic Compounds, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:22, 3529-3536

To link to this article: http://dx.doi.org/10.1080/00397919508015487

SYNTHETIC COMMUNICATIONS, 25(22), 3529-3536 (1995)

A STRAIGHTFORWARD SYNTHESIS OF [3.3.0] BICYCLIC COMPOUNDS

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Abstract : *cis*-3-Aza- and 3-Oxo-bicyclo[3.3.0]octane were prepared in two steps from the corresponding 1,6-dienes.

We have been interested in the synthesis of [3.3.0] bicyclic coumpounds having a *cis*-ring junction, notably in connection with the preparation of target molecules such as the oral hypoglycemic gliclazide (**D**, with R = p-CH_3-C_6H_4-$SO_2NHCONH$-). Usual access to this aza-bicyclooctane structure involves (Scheme 1)*trans*-cyclopentanedicarboxylic acid **A** which is first epimerized, converted to the anhydride, then the imide, and finally reduced.[1]

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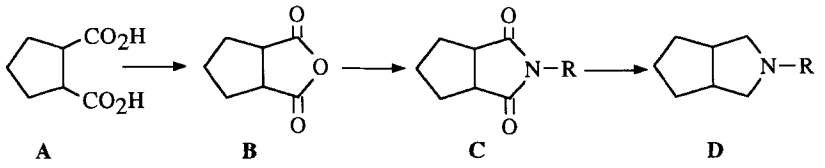


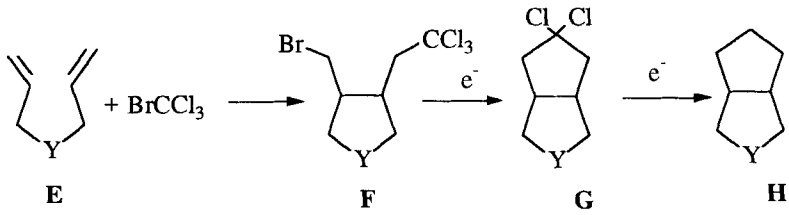
Scheme 1

The starting dicarboxylic acid **A** is not readily accessible[2] and we have previously investigated a possible electrochemical direct route to it from dimethyl maleate and 1,3-dibromopropane,[3] but we did not get a better than 50 % yield, *i.e.* comparable to the other routes.

We have now looked for an alternative straightforward approach involving the stereoselective ring closure of a linear reagent setting the potential *cis*-relation expected for the ring-junction in the final product. This can be obtained by a free radical ring closure of a 1,6-diene, since, according to Beckwith's rules,[4] a 1, 2 *cis*-disubstituted cyclopentanoid adduct is mainly formed. We then thought out the following reaction scheme (Scheme 2, with Y = NR), where the first step is the free-radical addition of $BrCCl_3$ to the N-protected diallylamine followed by reductive ring closure and reductive dehalogenation.

The first step (**E** → **F**) can be efficiently initiated by the thermal decomposition of AIBN (2,2'-azobis-(2-propionitrile)) in refluxing CCl_4 in the presence of **E** and $BrCCl_3$. We have already shown that such a free radical addition can also be initiated by a Mn(III)-promoted electrochemical approach.[5] Both methods led to 80% yield of isolated 3,4-substituted pyrrolidine, with Y = NCH_2Ph (**1**), in 4.5 *cis/trans* ratio. Surprisingly, the addition of CBr_4 to the N-benzyl-diallylamine was found to be less efficient (40 % of a 4.5 *cis/trans* mixture) than that of $BrCCl_3$.

The second step (**F** → **G**) is an electrochemical ring closure. The reaction was well conducted in DMF, in an undivided cell, in the presence of a sacrificial Zn-anode, from the *cis/trans* mixture of **1**. The consumption of the major *cis* **1**

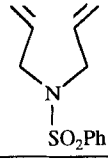
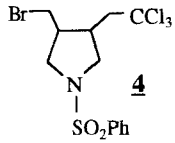
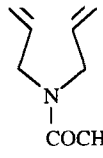
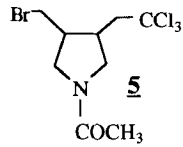
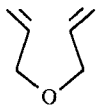
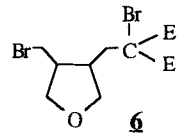
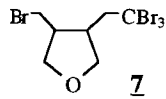
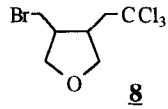
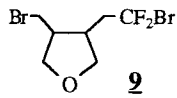


Scheme 2

was more rapid than for its isomer and only one bicyclic compound **2** was formed, and isolated in 70% yield. The reductive dehalogenation (**G** → **H**) leading to **3** was performed in acetonitrile by electrochemically activated zinc, in the presence of a proton donor; this step was nearly quantitative (>95%). Thus an overall yield of *ca.* 50% of *cis*-N-benzyl-3-azabicylo[3.3.0]octane (**3**) was obtained starting from the N-benzyl derivative **E**. The *cis* ring-junction was easily predicted on the basis of both Beckwith's rules and the higher rate of cyclisation of the major isomer, and was confirmed by ^{1}H and ^{13}C NMR analysis of **F**, **G**, and **H** compounds according to literature reference data for related compounds.[6] Yields of *ca.* 40 % of bicyclic **H** product were obtained with $PhSO_2$ or CH_3CO as N-protecting group in **E**.

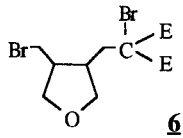
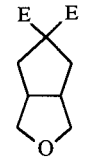
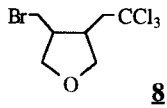
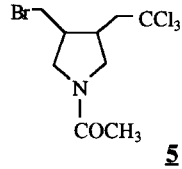
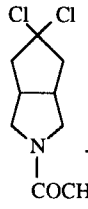
The method was also applied to various polyhalomethanes in the addition to diallylamine or diallyl ether (Scheme 2, Y = NR and O respectively). The reported results (table 1) have been obtained by the Mn(III)-promoted electrochemical method.[5] The formation of substituted pyrrolidines or furans (**E** → **F**) from the corresponding dienes is moderately to highly efficient. Some reactions were also conducted according to the usual free-radical method. Yields were found to be similar, but the great advantage of the electrochemical method is that it can be run at room temperature, which is quite advantageous in reactions involving CF_2Br_2. For all reactions the major product is the *cis*-isomer. The electroreductive cyclisation (**F** → **G**) was performed for some typical examples (table 2), and was not optimized.

Table 1 : Free-radical addition of polyhalomethanes to 1,6 dienes [a]

Diene	Halide	Product (yield %)
	$BrCCl_3$	 **4** (70) cis / trans = 4
	$BrCCl_3$	 **5** (65) cis / trans = 4
	Br_2CE_2 ($E = CO_2Me$)	 **6** (50) cis/trans = 4,5
	CBr_4	 **7** (76) cis/trans = 4,5
	$BrCCl_3$	 **8** (70) cis/trans = 5
	b) CF_2Br_2	 **9** (67) cis/trans = 5

[a] $Mn(OAc)_2$ (2 mmol), $NCCH_2CO_2CH_3$ (2 mmol), AcOH/AcOK (30 ml / 30 mmol) Diene (20 mmol), Halocompound (20 mmol), 60°C; [b] room temperature

Table 2 : Electroreductive cyclisation

Reagent	Product (Yield %)
 **6**	 (70) **10**
 **8**	 (69) **11**
 **5**	 (57) **13**

Adduct (10 mmol), DMF (30 ml), NBu_4Br (3 mmol), anode Zn, cathode inox, room temperature.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Brucker AC 200 E. Mass spectra were recorded obtained on a Finnigan ITD 800 spectrometer coupled to a Varian 300 chromatograph with a DB-1 capillary column, either by electron impact or with isobutane as the ionizing agent.

Radical addition of polyhalomethanes to 1,6-dienes

Method A (AIBN-initiated addition). A solution of the diene (20 mmol), the polyhalomethane (40 mmol), and 2,2'-azobis(2-methylproprionitrile) [AIBN] (1.8 mmol) in CCl_4 (40 ml) was refluxed until full consumption of the diene (usually ca 5 h). After filtration and vacuum removal of CCl_4, the product was isolated by silica gel column chromatography.

Method B (Mn-promoted electrochemical addition). A solution of $Mn(OAc)_2$ (2 mmol) in AcOH (30 ml) containing AcOK (30 mmol) was placed in an undivided electrochemical cell having two concentric electrodes made of carbon fiber (anode, 20 cm^2) and stainless steel (cathode) and first oxidized electrochemically to convert Mn(II) into Mn(III). The diene (20 mmol) and the halocompound were then added and the mixture was further electrolyzed for *ca.* 90 minutes at constant current intensity (I = 0.2 A). The solution was then evaporated under vacuum and the product isolated as above.

Electroreductive cyclisation : A solution of the monocyclic adduct (10 mmol) in DMF (30 ml) containing NBu_4Br (0.5 mmol) was placed in an undivided electrolytic cell fitted with a Zn-rod (anode) and a stainless steel grid (cathode, area; ca 20 cm^2). The solution was electrolyzed at constant current (I = 0.2 A) , at room temperature up to the complete disappearance of the starting compound (electricity required, ca 3 F/mol). After removal of DMF under vacuum and usual work up, the bicyclic product was isolated by chromatography on silica gel.

Reductive dehalogenation : A solution of 1,2-dibromoethane (3 mmol) in acetonitrile (30 ml) containing NBu_4Br (0.3 mmol) and NBu_4I (0.2 mmol) was electrolyzed in the presence of solid zinc as both anode and cathode material. The halogenated bicyclic compound (10 mmol) and propanoic acid (10 mmol) or MeOH (10 mmol) were then added to the electrolytic solution and allowed to react in the absence of current. A Zn(II)/Zn(0) redox system should account for the efficiency of this reductive dehalogenation process. Usual work up gave the expected product as nearly pure compound.

Identification of the Products.:

N-benzyl-3-bromoethyl-4-(2,2,2-trichloroethyl)pyrrolidine (1)

^1H NMR : 7.35 (m, 5H), 3.68 (d, 2H, d), 3.4 (m, 2H), 3.1 (m, 2H), 2.92-2.2 (m, 6H); ^{13}C NMR : cis-isomer 137, 99, 129, 128.3, 128.2, 127.5, 127.2, 59, 58, 57.7,

57.3, 42, 38, 33; trans-isomer 136.5, 129.6, 129, 128.6, 127.8, 98.7, 60, 59.4, 57.5, 53.6, 42.6, 41, 35 ; GC-MS (relative intensity) : 389-387-385 (M; 2, 4, 4.5), 310-308-306-304 (3, 15, 35, 35), 270-268 (5, 2), 91 (100), 65 (16)

N-benzyl-7,7-dichloro-3-azabicyclo[3.3.0]octane (2)

^{1}H NMR : 7.2 (m, 5H), 3.61-3.25 (m, 6H), 3.08-2 (m, 6H) ; ^{13}C NMR: 137, 129, 128.4, 128.2, 127.1, 126.9, 66.7, 58.8, 57.4, 53.9, 42.9, 41.6 ; GC-MS (relative intensity) : 271-269 (M; 14, 16.5), 236-234 (6, 26), 182-180-178 (3, 14, 15), 142 (12) ; 91 (100).

N-phenylsulfonyl-3-bromoethyl-4-(2,2,2-trichloroethyl)pyrrolidine (4)

^{1}H NMR : 7.7-7.4 (m, 5H), 3.8-3 (m, 6H), 2.64-2.4 (m, 4H) ; ^{13}C NMR : 136, 132.9, 129, 127.3, 127.1, 126, 98, 53.7, 51.1, 51, 43.9, 39.3, 30.3 ; GC-MS (relative intensity) 435 (M; 3), 355-353 (7, 11), 319-317 (5, 9), 179 (13), 141 (M-$SO_2C_6H_5$; 30), 77 (100).

N-acetyl-3-bromoethyl-4-(2,2,2-trichloroethyl)pyrrolidine (5)

^{1}H NMR : 3.4-2.8 (m, 6H), 2.7-2.3 (m, 4H), 1.6 (s, 3H) ; ^{13}C NMR : 169, 98, 53, 51.6, 50.8, 44.2, 39.7, 31.2, 22 ; GC-MS (relative intensity) : 339-337-335 (M; 31, 37, 35), 260-258 (42, 14), 243 (23), 218-216-214 (M-CCl_3; 47, 88, 84)

3-bromomethyl-4-[(2-bromo-2,2 dicarboxymethyl)ethyl]tetrahydrofurane (6)

^{1}H NMR :3.8 (m, 2H), 3.7 (s, 6H), 3.4 (m, 4H), 2.4 (m, 4H) ; ^{13}C NMR : 166.8 ; 166.7, 71.6, 70.4, 61, 53.89, 53.84, 44.6, 39.3, 35.3, 31; GC-MS (relative intensity) : 388 (M; 2), 229 (5.6), 177 (9.6), 145 ($C_6O_4H_9$, 100), 113 (37), 69 (20), 59 (22).

dimethyl 3-oxabicyclo[3,3,0] octane-7,7-dicarboxylate(10)

^{1}H NMR ($CDCl_3$) : 3.65 (s, 3H) , 3.64 (s, 3H) , 3.5 (m, 2H) , 2.7-2.5 (m, 2H) , 1.88 (m, 1H) ; ^{13}C NMR : 172, 73, 72.5, 53.8, 52.4, 44.6, 43.2, 41.2, 40 ; GC-MS (relative intensity) : 197 (11), 168 (37), 140 (40), 100 (59), 108 (18), 79 (77), 69 (100) ; Anal. Calcd for $C_{11}H_{16}O_5$ C, 57.88 ; H, 7.06 ; O, 35.5. Found : C, 57.34 ; H, 6.22 ; O, 34.71.

7,7-dichloro-3-oxabicyclo[3.3.0]octane (11)

^{1}H NMR : 3.67-3.48 (m, 2H), 2.8 (m, 2H), 2.08 (m, 1H) ; GC-MS (relative intensity) : 185-183-181 (1, 10, 16), 147-145 (10, 40), 115 (13), 91 (17), 83-81-79 (4, 50, 43), 69 (100).

N-acetyl-7,7-dichloro-3-oxabicyclo[3.3.0]octane (12)

^{1}H NMR : 3.8-3.3 (m, 6H), 2.2-3.3 (m, 4H), 2.1 (s, 3H) ; ^{13}C NMR : 169, 53.9,

57.2, 52, 50, 41.5, 39.8 ; GC-MS (relative intensity) : 223-221 (25, 11.6), 188-186 (42, 50), 144 (22), 110 (67), 77 (26), 68 (85), 45 (100).

The following compounds were identified by comparison of their spectral data with those given in the cited references :
N-benzyl-3-azabicyclo[3.3.0]octane (**3**);[9] 3-bromomethyl-4-(2,2,2-tribromoethyl)-tetrahydrofurane (**7**);[5] 3-bromomethyl-4-(2,2,2-trichloroethyl)tetrahydrofurane (**8**);[7] 3-bromomethyl-4-(2,2-difluoro-2-bromoethyl)tetrahydrofurane (**9**).[8]

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(Received in the UK 29 March 1995)