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LETTERS

An Effective Regioselective Electrophilic Halogenation of Tricyclo[5.2.1.$0^{2,6}$]decenyl Enaminones

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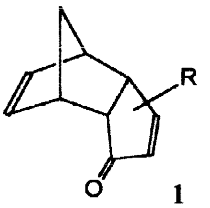
Abstract: 5-Amino-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ones **4** undergo a surprisingly effective regioselective halogenation using N-halosuccinimides (NXS) under electrophilic conditions. Exclusive α–halogenation is observed using one equiv. of NXS, whereas, either α,γ– or α,N-bishalogenation products are formed in quantitative yields when an additional equiv. of NXS is applied. Most importantly, halogenation of the C_8-C_9 norbornene bond is not observed.

Tricyclic structures **1** serve as synthetic equivalents of cyclopentadienones[1] and as such enable the synthesis of substituted cyclopentenones *e.g.* **2**[2]. The basic strategy involves regio- and stereoselective functionalization of **1**, eventually followed by thermal [4+2]-cycloreversion. In principle, this strategy can also be applied for the synthesis of halo-containing cyclopentenoids, a class of compounds which is not only of synthetic interest but also exhibits promising biological properties. Examples are naturally occurring marine prostanoids halovulones **3**[3] and related punaglandins[4] which show remarkable cytotoxicity[5]. An effective route to halo-cyclopentenoids requires a highly regioselective halogenation of the tricyclodecadienone system at the cyclopentenone moiety whereby halogenation of the C_8-C_9 norbornene double bond in **1** must be avoided. This double bond is pivotal for the eventual thermal [4+2]-cycloreversion step. Recently, we reported an efficient and diastereoselective synthesis of 5-amino-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ones **4** and their use for the synthesis of homochiral 4-aminocyclopentene-2-ones **2**.[2,6] These tricyclic enaminones **4** may be excellent starting substrates to meet this requirement of selective halogenation at the enone moiety as the β-enaminone moiety is susceptible to electrophilic addition because of the electron release by the β-amino function. In this communication, we disclose an efficient regioselective monohalogenation of tricyclic enaminones **4** and an unprecedented bridgehead halogenation during dihalogenation.



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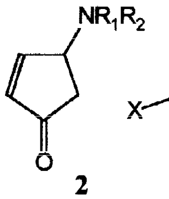

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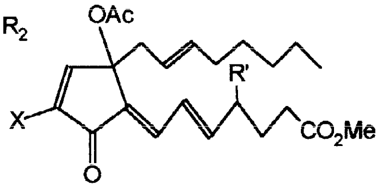
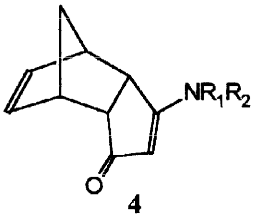


3 X= Cl, Br, I



4

Halogenation of enaminones to obtain α-halo enaminones, has been carried out with a variety of reagents such as bromine,[7] iodine,[8] N-bromosuccinimide,[7] cyanogen bromide,[7] benzyltriethylammonium trichloroiodate.[9,10] In order to minimize halogenation of the C_8-C_9 double bond in **4** we selected N-halosuccinimides as the most promising reagents. The reaction of tricyclic enones **4** with 1 equivalent of N-

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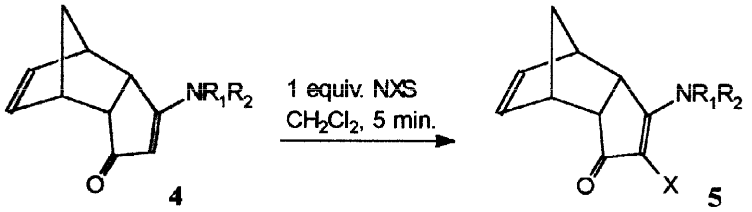
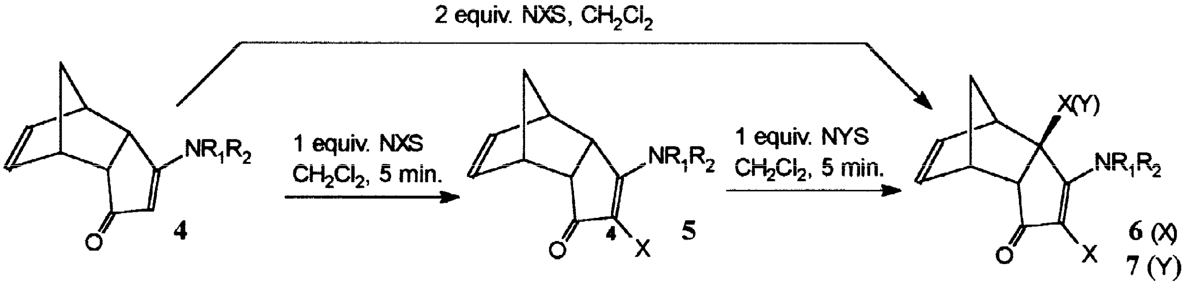
chloro, N-bromo or N-iodosuccinimides in dichloromethane at room temperature appeared to be extremely fast and efficient. Within 5 minutes complete conversion of **4** was observed to give single monohalogen compounds in almost quantitative yields (Scheme 1). Spectral analysis revealed that these products are the desired tricyclic α-halo enaminones **5**. Both their yields and rates of formation appeared to be independent of the nature of amino substituent, being either secondary or tertiary. No products derived from halogenation of the C_8-C_9 double bond were detected. In contrast to a literature report,[10] polyhalogenation of **4** was not observed. However, polybromination took place when elemental bromine was used instead of N-bromosuccinimide (NBS). The observation that no halogenation takes place at the C_8-C_9 double bond seems typical for **4** as this norbornene type double bond is usually rather reactive towards N-halosuccinimides[11]. Replacing dichloromethane as a solvent by methanol to trap a conceivable transient C_8-C_9 bromonium ion did not lead to any addition product, proving the inertness of the C_8-C_9 double bond in tricyclic enaminones **4** toward electrophilic halogenation.



Scheme 1

Compound	Amine	Product	X	Yield(%)
4a	benzylamine	**5a**	Br	97
4b	cyclohexylamine	**5b**	Br	98
4c	n-pentylamine	**5c**	Br	97
4d	pyrrolidine	**5d**	Br	98
4e	S-(+)-prolinol	**5e**	Br	93
4f	R-(+)-α-methylbenzylamine	**5f**	Br	98
4a	benzylamine	**5g**	Cl	97
4d	pyrrolidine	**5h**	Cl	98
4i	S-(+)-prolinol methyl ether	**5i**	I	86

An unexpected result was obtained when the halogenation of **4** was carried out with two equivalents of N-halosuccinimide. Treating tertiary enaminone **4d** with two equivalents of NBS in dichloromethane a fast dibromination took place to afford α,γ-dibromo enaminone **6a** in quantitative yield (Scheme 2). In a similar way, α,γ-dichloro enaminone **6b** was obtained albeit at a lower rate, using NCS in methanol. The same result was obtained when the halogenation of **4d** was carried out in a step wise manner by reacting monohalo compounds **5d** and **5h** with an additional equivalent of N-halosuccinimide. Using this procedure mixed α,γ-dihalotricyclic enaminones **7a** and **7b** could also be obtained using different N-halosuccinimides in any of the two steps (Scheme 2).

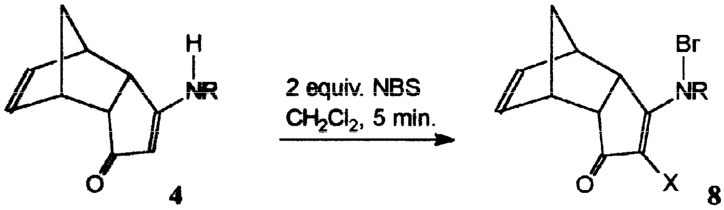


Scheme 2

Compound	Amine	NXS	NYS	Solvent	Reaction time	Product	Yield (%)
4d	pyrrolidine	Br		CH_2Cl_2	10 min	**6a**	99
4d	pyrrolidine	Cl		MeOH	1 day	**6b**	82
4a	benzylamine	Cl		CH_2Cl_2	1 day	**6c**	80
4b	cyclohexylamine	Cl		CH_2Cl_2	1 day	**6d**	90
4d	pyrrolidine	Br	Cl	CH_2Cl_2	10 min	**7a**	99
4d	pyrrolidine	Cl	Br	CH_2Cl_2	10 min	**7b**	94

In contrast to the monohalogenation of **4**, the nature of the amino substituent plays a decisive role in the second halogenation step. When secondary enaminones, such as **4a**, **b**, **c** and **f**, were treated with 2 equivalents of NBS, under identical conditions as applied for the tertiary enaminones, dibromination again occurred readily, however, now the second bromine was introduced exclusively at nitrogen to give quantitatively α-bromo-N-bromo enaminones **8** (Scheme 3). This N-halogenation of secondary enaminones **4** is a rather subtle process as is indicated by the result of the reaction of two equivalents of NCS with **4a** and **b** (Scheme 2). Here, no N-chlorosubstitution was observed at all but exclusive substitution at the bridgehead C_6 position had taken place to give **6c** and **d**, respectively.

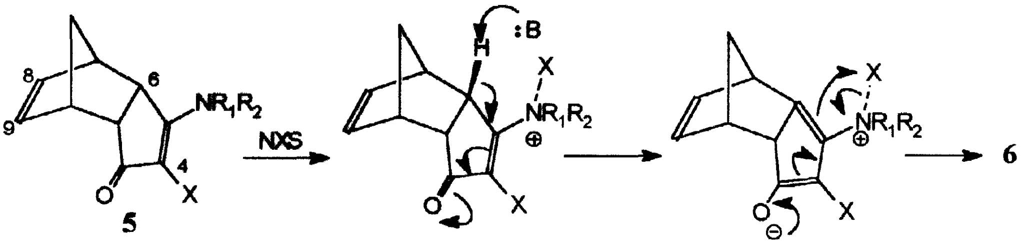
α-Haloenaminones **5** are formed in an enamine type addition reaction followed by release of the C_4-proton. Initial N-halogenation cannot be excluded but if occurring, the resulting N-halo compound is not stable and readily releases the halonium ion to form the more stable halide **5**. This is true for both the secondary and tertiary enaminones. However, after the introduction of the halogen at the C_4-position, this position is apparently deactivated in such a way that halogenation at other nucleophilic sites becomes competitive. The observation that secondary α-halo enaminones such as **5a**, **b**, **c** and **f** give rise to N-bromination with complete regioselectivity suggests that the initial step in the halogenation of both secondary and tertiary enaminones **5** involves initial reaction at nitrogen. In case of secondary enaminones a proton can readily be eliminated to form a relatively stable N-halo enaminone **8**. Obviously, such a proton elimination is impossible for tertiary enaminones and therefore an alternative reaction pathway is chosen which leads to halogenation at the γ-position in the enaminone moiety. The completely regioselective γ-halogenation can be rationalized by assuming that the C_6 hydrogen is relatively acidic as the result of the electron withdrawing effect of the C_4 halogen and the relatively high stability of thus formed cyclopentadienolate (Scheme 4). In this enolization process the N-succinimide anion most likely serves as the base. The observation that chlorination of secondary enaminones, such as **5a**,**b**, with NCS leads again exclusively to α,γ-dichloro enaminones **6c**,**d**, respectively, supports this rational as the N-chloro



Scheme 3

Compound	Amine	Product	Yield(%)
4a	benzylamine	**8a**	97
4b	cyclohexylamine	**8b**	98
4c	n-pentylamine	**8c**	97
4f	(R)-(+)-α-methylbenzylamine	**8f**	98

compounds are presumably less stable than the corresponding N-bromo compounds and therefore are more prone to rearrange to the thermodynamically more stable dichloroenaminone **6c** and **6d**.



Scheme 4

The complete inertness of the C_8-C_9 bond in these halogenation reactions is quite remarkable. It may be hypothesized that in these *endo*-5-aminotricyclodecadienones **4** there is considerable orbital interaction between the enaminone π-system and the C_8-C_9 double bond which decreases the nucleophilicity of the latter olefinic bond. The observed complete regioselectivity for the electrophilic halogenation of enaminones **4** is a highly relevant finding as an intact C_8-C_9 double bond is a prerequisite in our synthetic route to cyclopentenoids.

In conclusion, we have discovered that 4-aminotricyclodecadienones **4** can be regioselectively halogenated to give 4-halo-5-amino-, 4,6-dihalo-5-amino, and 4,N-dihalo-5-amino-tricyclodecadienones **5**, **6** and **7**, and **8**, respectively, in excellent yields. Besides the intriguing mechanistic aspects of these halogenation reactions, the resulting halogenated tricyclic enaminones allow further functionalization of the tricyclodecadienone system and therefore are promising precursors for pharmacologically interesting (halo)-cyclopentenoids. In particular the unprecedented formation of the C_6 substituted halo compounds **6** and **7** offers good synthetic prospects as these bridgehead halo substituted tricyclodecadienones are suitable synthons for β-functionalized cyclopentenoids. The synthesis of the antibiotic kjellmanianone, which has recently been carried out in our laboratory is an illustrative example of such an application[12].

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