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New synthetic methodology for 3-aminotropones

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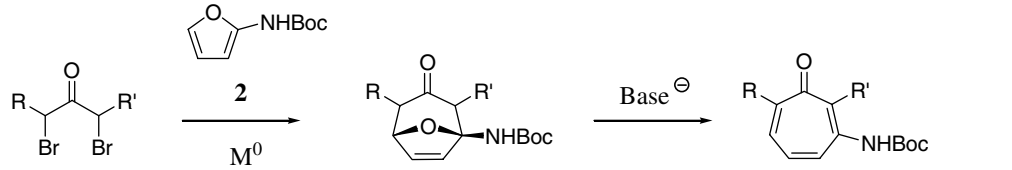
Abstract—A new synthetic methodology for 3-aminotropones is described. Tropones and 3-aminotroponic building blocks, present in a number of active natural products, could be prepared by a two step synthetic pathway: a first step consisting in a [4+3] cycloaddition reaction between a conveniently substituted α,α′-dihaloketone and a furan derivative functionalized on C-2 by a protected amino group. The second step is based on a rearrangement of the cycloadduct, via the cleavage of the oxygen bridge, under basic conditions.

The tropone ring system is a common structural motif in a wide array of natural products, ranging from simple monocyclic systems[1] to more complex alkaloids.[2] The broad range of biological properties of these compounds has stimulated important synthetic efforts, with the formation of the cycloheptatriene system being the pivotal synthetic objective.

Different approaches to the synthesis of the tropone ring have been carried out on the basis of different cycloaddition reactions[3] or by a cyclohexane ring expansion[4] as a key step. Nevertheless, appropriately substituted tropones are not easily synthesized, because the specific introduction of substituents at desired positions is hard to achieve. In particular, only two syntheses of 3-aminotropones have been published.[5,6] Moreover, these 3-aminotropones are not substituted. Therefore, the development of new general and direct routes to substituted aminotropones is worthwhile.

In the present work we report a new, versatile and short synthesis of 3-aminotropones substituted on C2 and/or C5 in only two steps: (a) a [4+3] cycloaddition reaction between a conveniently substituted α,α′-dihaloketone and a furan derivative[7] functionalized on C-2 by a protected amino group and (b) a rearrangement of the cycloadduct under basic conditions.

In particular, the cycloadducts, 1-*tert*-butoxycarbonylamino-8-oxabicyclo[3.2.1]oct-6-en-3-ones (Scheme 1)



1a, R= CH_3 R'= CH_3
1b, R= CH_2-CH_3 R'= CH_3
1c, R= CH_2-CH_3 R'= CH_2-CH_3

3a, R= CH_3 R'= CH_3
3b, R= CH_2-CH_3 R'= CH_3
R= CH_3 R'= CH_2-CH_3
3c, R= CH_2-CH_3 R'= CH_2-CH_3

4a, R= CH_3 R'= CH_3
4b, R= CH_2-CH_3 R'= CH_3
R= CH_3 R'= CH_2-CH_3
4c, R= CH_2-CH_3 R'= CH_2-CH_3

Scheme 1. Synthetic pathway for the preparation of 3-aminotropones **4a**–**c**. See Tables 1 and 2 for stereochemistry definition of compounds **3a**–**c**.

Keywords: [4+3] cycloaddition; 3-Aminotropones; 8-Oxabicyclo[3.2.1]oct-6-en-3-one; Oxygen bridge cleavage; Rearrangement under basic conditions.
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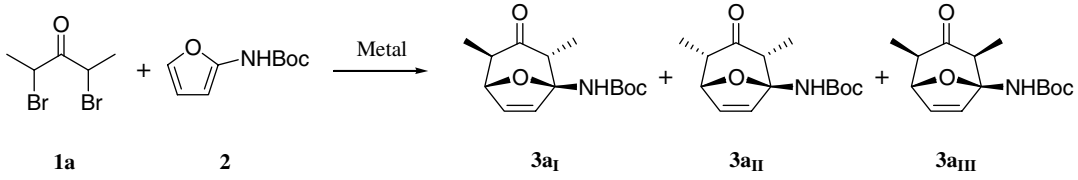
were prepared by a [4+3] cycloaddition reaction[8] between 2-*tert*-butoxycarbonylamino-furan **2** and an oxyallyl cation generated, in situ, from α,α′-dibromo-ketones **1** and a reducing metal (M^0).[9]

The starting materials **1a–c** were easily accessible in one step and in moderate to good yields from their corresponding ketones, through bromination under PBr_3 catalysis. Compound **2** was easily obtained from 2-furoyl chloride and sodium azide in *tert*-butanol through a Curtius rearrangement in excellent yield.[10] Pure diastereoisomeric oxabicycles **3a–c** were readily available from **1a–c** and **2** by a [4+3] cycloaddition reaction[11] followed by flash column chromatography. The rearrangement of the bicyclic compounds **3a–c** in the presence of a base generated the 3-aminotropones **4a–c**.

First of all, we studied the reaction between **1a** and **2** in order to optimize the reaction conditions (Scheme 2).



1a **2** **3a$_I$** **3a$_{II}$** **3a$_{III}$**

Scheme 2. [4+3] cycloaddition reaction between **1a** and **2**.

Table 1. Optimization of reaction conditions of the [4+3] cycloaddition between **1a** and **2**

Entry	Metal	Molar ratio (metal/**2**)	Solvent	*T* (°C)	Reaction time (h)	Yield (%)[a]	DAS **3a$_I$**/**3a$_{II}$**/**3a$_{III}$**
1	Cu	4/1	ACN	−10 then rt	4.5	33	2/52/46
2	Cu+NaI	4+8/1	ACN	−10 then rt	4.5	47	0/51/49
3	Zn	4/1	ACN	−10 then rt	22	15	30/58/12
4	Zn+NaI	4+8/1	ACN	−10 then rt	22	62	25/42/33
5	Zn+ClTMS	4+1.2/1	ACN	−10 then rt	4.5	0	—
6	Zn/Cu	97.7 mg metal/mmol diene	ACN	−10 then 0	4.75	18	28/61/11
7	Zn/Cu	97.7 mg metal/mmol diene	ACN	−10 then rt	4.75	33	38/55/7
8	Zn/Cu+NaI	97.7 mg metal/mmol diene	ACN	−10 then rt	4.5	37	8/46/46
9	$Fe_2(CO)_9$	1.75/1	Benzene	−10 then reflux	5.5	0	—
10	$Fe_2(CO)_9$	1.75/1	ACN	−10 then rt	6.5	76	55/40/5

[a] On isolated product by column chromatography.

Table 2. [4+3] cycloaddition reactions between **1a–c** and **2**

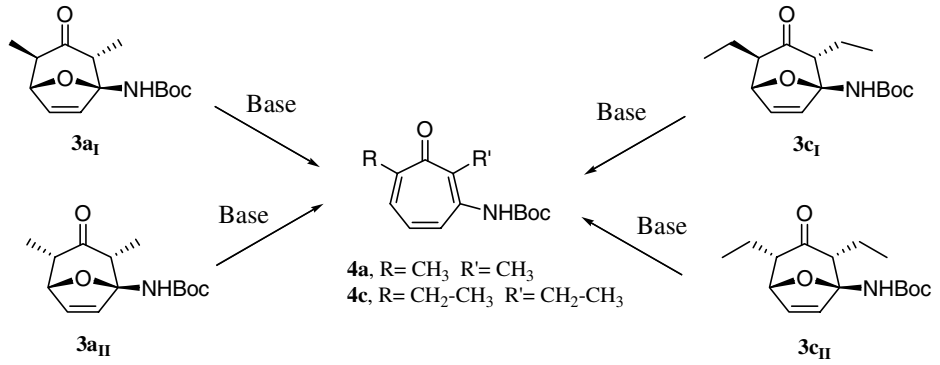
Entry	Substrate	Reaction time (h)	Yield (%)[a]	Products	DAS
1	**1a**	6.5	76	**3a$_I$**, **3a$_{II}$**, **3a$_{III}$**	55/40/5
2	**1b**	7	55	**3b$_I$**, **3b$_{II}$**, **3b$_{III}$**, **3b$_{IV}$**	30/24/25/21
3	**1c**	7	60	**3c$_I$**, **3c$_{II}$**	52/48

[a] On isolated product by column chromatography.

The results obtained from the [4+3] cycloaddition reactions are quoted in Table 1. From these data it was possible to conclude that the best yield could be achieved by using $Fe_2(CO)_9$ as a reducing agent in anhydrous acetonitrile. When using a reducing metal or a metallic pair, except for $Fe_2(CO)_9$, the presence of NaI improved the reaction yields, due to the fact that diiodoketones, which are generated in situ from dibromoketones and NaI, are more reactive than dibromoketones. The diastereoselectivity of cycloadducts was affected by the nature of the metal. Thus, $\mathbf{3a}_{III}$ was obtained in higher proportion by using Cu in the presence of NaI, and $\mathbf{3a}_{I}$ with the use of $Fe_2(CO)_9$.

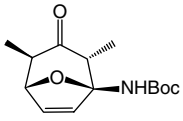
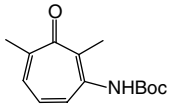
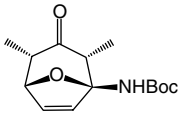
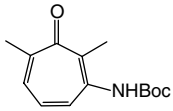
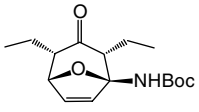
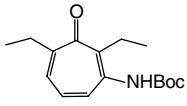
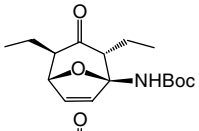
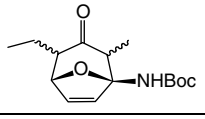
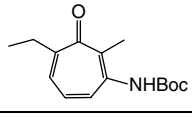
The optimized [4+3] cycloaddition reactions of the evaluated substrates were carried out under similar conditions (see Table 2): using $Fe_2(CO)_9$ as a reducing agent and anhydrous acetonitrile as a solvent. In all cases the reaction was run at room temperature after the slow addition of dibromoketone at −10 °C. All obtained diastereoisomeric products were separated and purified by column chromatography, and they were physically and spectroscopically characterized. In Table 2 quoted are the results obtained from all the performed [4+3] cycloaddition reactions.

When pure diastereoisomeric oxabicycles **3a–c** were treated with a base, all of them underwent a molecular rearrangement to generate in one step 3-aminotropones **4a–c**. In addition, pure diastereoisomeric bicycles $\mathbf{3a}_{I}$ and $\mathbf{3a}_{II}$ afforded, in identical reaction conditions, the same product **4a**. In a similar way, $\mathbf{3c}_{I}$ and $\mathbf{3c}_{II}$ generated independently the product **4c** (Scheme 3). Thus, the formation of 3-aminotropones from C1-amino-functionalized



Scheme 3. Formation of 3-aminotropones **4a** and **4c** from oxabicycles $\mathbf{3a}_{I–II}$ and $\mathbf{3c}_{I–II}$, respectively, under basic conditions.

Table 3. Reaction conditions of the rearrangement of cycloadducts **3a–c** to afford 3-aminotropones **4a–c**

Entry	Substract	Base	Molar ratio (base/substract)	Solvent	Reaction time (h)	Observations	Product	Yield[a] (%)
1		NaOH	2	MeOH anh	168	—		30
2		TTBAL-H	4	EtOH abs	72	—		70
3		NaOH	2	MeOH anh	168	—		30
4		$NaNH_2$	2	THF anh	6	—		21
5		^tBuOK	4	THF anh	2	—		54
6		TTBAL-H	4	THF anh	7	Ketone reduction was observed		0
7		TTBAL-H	4	MeOH anh	48	—		0
10		TTBAL-H	4	EtOH abs	4	Ultrasound		70
11		TTBAL-H	5	EtOH abs	4	Ultrasound		61
12		TTBAL-H	5	EtOH abs	4	Ultrasound		60
13		TTBAL-H	5	EtOH abs	4	Ultrasound		69

[a] Calculated by ^1H NMR on the reaction product, just after the workup. The yields calculated on isolated product by column chromatography decreased 10% due to decomposition of 3-aminotropones.

8-oxabicyclo[3.2.1]oct-6-en-3-ones proved to be general and the product obtained was the same regardless the configuration at C2 or at C4 in oxabicyclic cycloadducts.

Reaction conditions and results in the obtention of 3-aminotropones from C1-amino-functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-ones are shown in Table 3. The studied parameters were: type of base (NaOH, $NaNH_2$, ^{t}BuOK and lithium tri(*tert*-butoxy)-aluminium hydride TTBAL-H), molar ratios and nature of solvent (protic and aprotic). From these data it was possible to conclude that the best results were achieved by using TTBAL-H as a base in absolute ethanol and in an ultrasound reactor. The use of NaOH and $NaNH_2$ (entries 1, 3 and 4) afforded the same product but in lower yields and with slower kinetics than in the case of using ^{t}BuOK and TTBAL-H. The reaction was usually performed in an ultrasound reactor in order to accelerate the reaction. All new 3-aminotropones were isolated and purified by column chromatography and physically and spectroscopically characterized. 3-Aminotropones proved to be oxygen and light sensitive, thus when they were submitted to column chromatography in order to obtain very pure samples for their characterization, decomposition was observed. So, the yields after chromatographic purification were 10% lower than those calculated by ^{1}H NMR on the reaction product, just after the workup. Efforts to overcome this problem are underway in our laboratory.

In summary, we have studied the [4+3] cycloaddition reaction between C2-amino-functionalized furan **2** and α,α′-dibromoketones **1a–c** to obtain oxabicycles **3a–c**, in moderate to good yields, by a [4+3] cycloaddition reaction mediated by $Fe_2(CO)_9$, as a reducing agent, in anhydrous acetonitrile. Moreover, we have studied the rearrangement of oxabicycles **3a–c** mediated by a base, to afford 3-aminotropones **4a–c**. At the present moment, we are carrying out additional studies in order to propose a mechanism for the 3-aminotropone formation. We are also working on the development of a more general methodology that should allow us to obtain a wide range of mono, di and trisubstituted 3-aminotropones, starting from a series of structurally different C2-aminofurans at the level of the [4+3] cycloaddition reaction.

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