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Synthesis of 2-Azaspiro[4.6]undec-7-enes from N-Tosyl-N-(3-arylpropargyl)-Tethered 3-Methylcyclohex-2-en-1-ols

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ABSTRACT: The $FeCl_3$-promoted synthesis of 2-azaspiro[4.6]-undec-7-ene rings proceeds via ring expansion/cyclization/chlorination of *N*-tosyl-*N*-(3-arylpropargyl)-tethered 6-methylbicyclo[4.1.0]heptan-2-ols. This azaspirocyclic ring skeleton can also be obtained in one pot from the *tert*-butyldimethylsilyl-protected *N*-tosyl-*N*-(3-arylpropargyl)-tethered 3-methylcyclohex-2-en-1-ols and diethylzinc/diiodomethane.

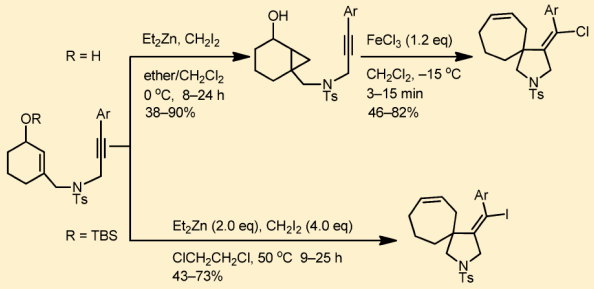
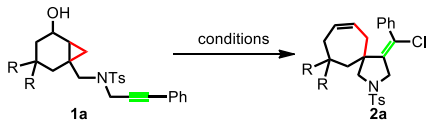


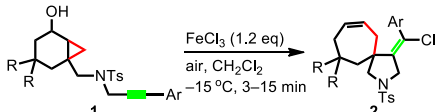
Table 1. Optimization of the Ring Expansion/Cyclization/Chlorination of 1a to 2a



entry	acid	solvent	temp (°C)	time	yield (%)[a]
1	$FeCl_3$	CH_2Cl_2	30	1 min	63
2	$FeCl_3$	CH_2Cl_2	0	3 min	73
3	$FeCl_3$	CH_2Cl_2	−15	3 min	82
4	$FeCl_3$	CH_2Cl_2	−78	4 h	75
5	$FeCl_3 \cdot 6H_2O$	CH_2Cl_2	30	50 min	70
6	$TiCl_4$	CH_2Cl_2	−15	1 min	67
7	$InCl_3$	CH_2Cl_2	30	25 min	54
8	$ZnCl_2$	CH_2Cl_2	30	1 h	49
9	(TMS)Cl	CH_2Cl_2	30	24 h	0
10	$Fe(OTf)_3$[b]	MeOH	30	24 h	0
11	HCl(aq)[c]	CH_2Cl_2	−15	10 min	10
12	$FeCl_3$	DCE	−15	1 min	35
13	$FeCl_3$	DBE	30	1 min	52
14	$FeCl_3$	DBM	−15	1.5 h	80
15	$FeCl_3$	CH_3CN	30	24 h	0

[a] All reactions were conducted using 0.1 M **1a** and 1.2 molar equiv of acids in the air, and yields were obtained by flash column chromatography. [b] A catalytic amount (10 mol %) of $Fe(OTf)_3$ was used. [c] An excess amount of HCl(aq) was used.

Scheme 1. Iron Trichloride-Promoted Synthesis of Azaspiro[4.6]undecene Derivatives 2



a : Ar = phenyl, R = H 82%
b : Ar = 4-methylphenyl, R = H 58%
c : Ar = phenyl, R = CH_3 80%
d : Ar = 4-methylphenyl, R = CH_3 63%
e : Ar = 4-bromophenyl, R = H 77%
f : Ar = 4-bromophenyl, R = CH_3 70%
g : Ar = 3-carbethoxyphenyl, R = H 46%
h : Ar = 3-methoxyphenyl, R = H 77%

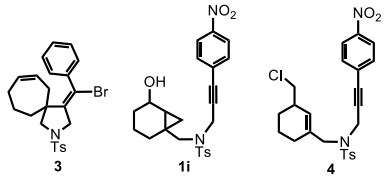
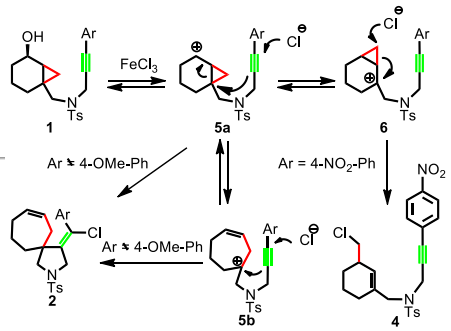
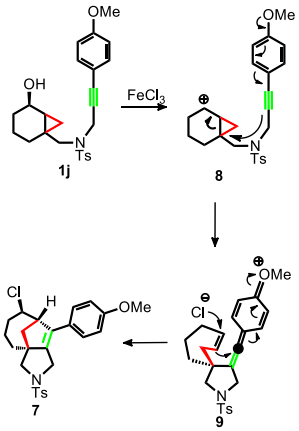


Figure 1. Compounds 3, 1i, and 4.

Scheme 2. Plausible Mechanism for Formation of 2 and 4



Scheme 3. Plausible Mechanism for the Formation of Compound 7



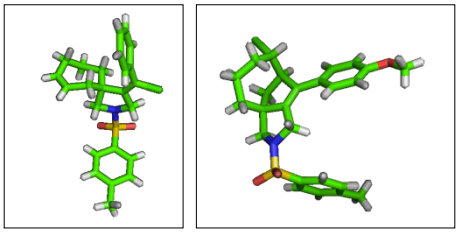
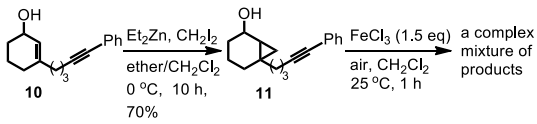
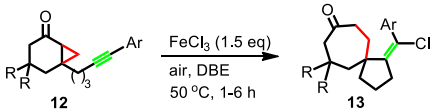


Figure 2. X-ray crystallographic structures of 2a and 7

Scheme 4. Reaction of Compound 11 with Iron Trichloride

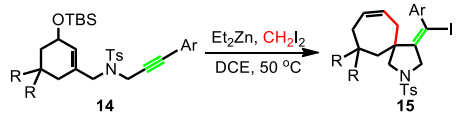


Scheme 5. Iron Trichloride-Promoted Synthesis of Spiro[4.6]undecan-8-ones 13



a : Ar = phenyl, R = H 50%
b : Ar = 4-methylphenyl, R = H 46%
c : Ar = 3-methoxyphenyl, R = H 45%
d : Ar = phenyl, R = CH_3 62%
e : Ar = 4-methylphenyl, R = CH_3 53%
f : Ar = 3-methoxyphenyl, R = CH_3 60%

Table 2. One-Pot Process for the Construction of Azaspiro[4.6]undecene Derivatives 15[a]



entry	substrate	R	Ar	time (h)	yield (%)
1	**14a**	H	phenyl	9	43 (**15a**)
2	**14b**	H	4-methylphenyl	25	46 (**15b**)
3	**14c**	H	4-bromophenyl	20	56 (**15c**)
4	**14d**	CH_3	phenyl	12	73 (**15d**)
5	**14e**	CH_3	4-methylphenyl	11	48 (**15e**)
6	**14f**	CH_3	4-bromophenyl	12	57 (**15f**)
7	**14g**	CH_3	3-methoxyphenyl	9	59 (**15g**)
8	**14h**	CH_3	4-phenylphenyl	9	47 (**15h**)

[a] All reactions were run in dried DCE under nitrogen, and yields were obtained after flash column chromatography.

Scheme 6. Diethylzinc/Diiodomethane-Promoted Synthesis of Azatricycle 16