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Dibenzoxazepinium Ylides: Facile Access and 1,3-Dipolar Cycloaddition Reactions

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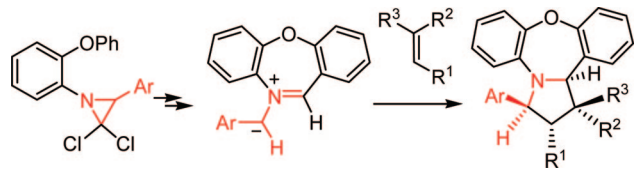
ABSTRACT



An effective approach to azirino-fused heterocycles is disclosed. The approach, involving formation of heterocycle/*C*-(arylchloromethyl)-subsituted *C*═N double bond via domino isomerization of a *gem*-dichloroaziridine−intramolecular Friedel−Crafts acylation of the *O*-tethered benzene ring and subsequent intramolecular cyclization induced by hydride, was realized for 1-aryl-1,11b-dihydroazirino[1,2-*d*]dibenz[*b*,*f*][1,4]oxazepines. The latter are excellent precursors of azomethine ylides, especially in solvent-free conditions, which can undergo a completely stereoselective 1,3-dipolar cycloaddition to C═C dipolarophiles giving derivatives of dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine.

Dibenz[*b*,*f*][1,4]oxazepine derivatives are attractive compounds of growing pharmaceutical interest as documented by many publications. Among compounds containing this fragment are a non-nucleoside HIV-1 reverse transcriptase inhibitor,[1] a histamine H_4 receptor agonist,[2] calcium[3] and PGE_2 antagonists,[4] as well as antidepressants[5] and analgesics.[4] Compounds with nitrogen heterocycles *ortho*-fused to dibenz[*b*,*f*][1,4]oxazepine also demonstrate various forms of bioactivity: derivatives of dibenzo[*b*,*f*]pyrimido[3,4-*d*][1,4]-oxazepine show antidepressive and anxiolytic activity,[6] derivatives of dibenz[*b*,*f*]imidazo[1,5-*d*][1,4]oxazepine are useful in pharmaceutical compositions for treating bronchial asthma and allergic bronchitis,[7] 2,7-dimethyl-1,3,4,14b-tetrahydro-2*H*-dibenzo[*b*,*f*]pyrazino[1,2-*d*][1,4]oxazepine shows

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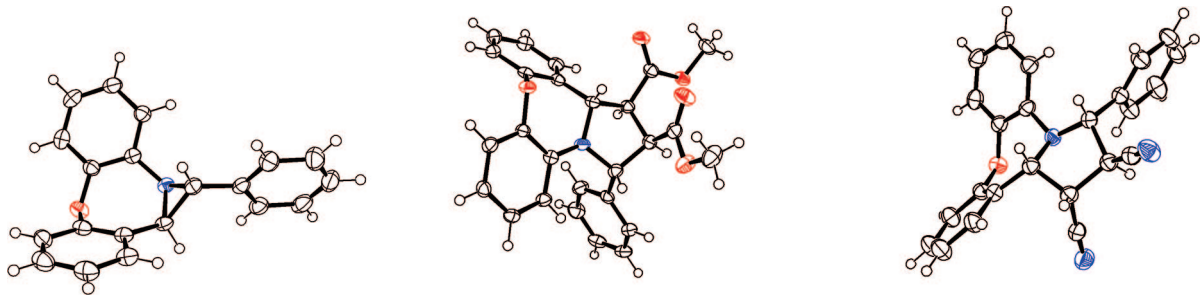
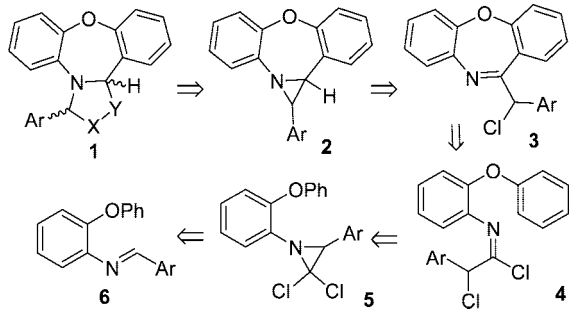


Figure 1. ORTEP representation of compounds **8a**, **19**, and **20**.

antiserotoninergic and antihistaminic effects,[8] and 2,3,4,14b-tetrahydro-1*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]oxazepines are progesterone receptor agonists.[9] Approaches to potentially bioactive heterocycles with a pyrrole ring *ortho*-fused to dibenz[*b*,*f*][1,4]oxazepine have been until now unknown.

Due to our research interest concerning the synthesis of nitrogenated heterocycles via nitrogen ylide reactions,[10] we envisioned the possibility of assembling a new heterocyclic system—dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine—according to the retrosynthetic sequence described in Scheme 1.

Scheme 1



The key step in the scheme is the formation of the dibenz[*b*,*f*]-[1,4]oxazepine skeleton concurrently with an ArCHCl group (compound **3**). This could potentially be realized via an intramolecular Friedel—Crafts acylation of the *O*-tethered benzene ring by 2-aryl-2-chloroacetimidoyl chlorides, which in turn can be generated from *gem*-dihaloaziridines.[11] 1,3-Diaryl-2,2-dichloroaziridines are readily available via reaction of imines with dichlorocarbene. The synthesis of compounds **5** was performed by reaction of imines **6** with dichlorocarbene generated from $CHCl_3$ and solid KOH in the presence of TEBA as phase-transfer catalyst at 19—21 °C.

gem-Dichloroaziridines isomerize to imidoyl chlorides under the action of Lewis acids,[10i] which are well-known catalysts of Friedel—Crafts acylation. Hence, we tried to realize aziridine ring opening and intramolecular Friedel—Crafts acylation in a domino reaction. We tested $BF_3{\cdot}Et_2O$, $TiCl_4$, and anhydrous $AlCl_3$ as catalysts. It was found that with $BF_3{\cdot}Et_2O$ or $TiCl_4$ as catalyst the reaction of aziridine **5a** proceeded very slowly at 50 °C and long reaction times were required at this temperature. This led to decomposition of the reaction mixtures and yields of the target compound were less than 10%. The Lewis acid of choice for the realization of target domino reaction proved to be $AlCl_3$, giving oxazepines **3a**,**b** in 59 and 68% yields (Scheme 2).

α-Chloroketimines when reacted with nucleophilic reagents give aziridines, but this approach was not used for the synthesis of the azirino-fused compounds.[12] The preparation of azirinodibenzoxazepines **8a**,**b** was performed by reduction of **3a**,**b** with $LiAlH_4$ in 70—90% yields. The ^1H NMR spectra of compounds **8a**,**b** exhibited the characteristic coupling constant value for *trans*-aziridines $J \sim 3$ Hz (J for *cis*- and *trans*-aziridines are 6—7 and 2.5—3.5 Hz, respectively[12a,13]). The structure of compound **8a** was confirmed by X-ray analysis (Figure 1).

Scheme 2

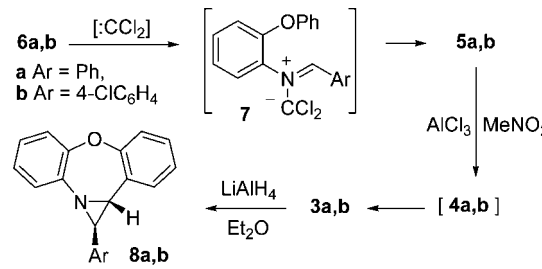


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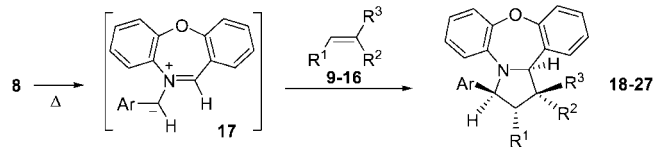
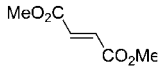
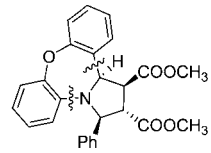
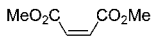
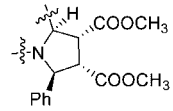
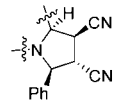
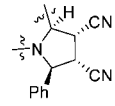
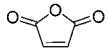
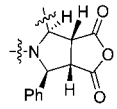
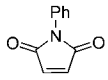
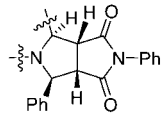
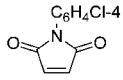
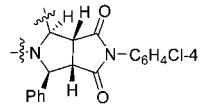
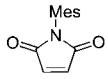
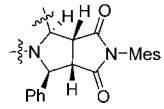
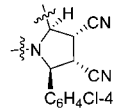
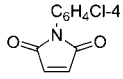
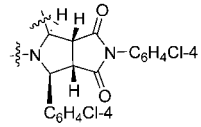
Table 1. Reaction of Aziridines **8a**,**b** with C=C Dipolarophiles **9**−**16**



entry	aziridine, **8**	dipolarophile		product		method[a]	time	yield,[b] (%)
1	**a**		**9**		**18**	A	7 h	94
2	**a**		**10**		**19**	A B	8 h 15 min	93 71
3	**a**		**11**		**20**	A B	7 h 15 min	88 76
4	**a**		**12**		**21**	A	7 h	94
5	**a**		**13**		**22**	A	8 h	94
6	**a**		**14**		**23**	A B	12 h 15 min	97 84
7	**a**		**15**		**24**	A	10 h	96
8	**a**		**16**		**25**	A	8 h	89
9 10	**b**		**12**		**26**	A B	6 h 10 min	94 95
11 12	**b**		**15**		**27**	A B	8 h 15 min	75 78

[a] A: toluene, 90 °C. B: melt, 140 °C. [b] Isolated yields.

It was found that heating aziridines **8a**,**b** in anhydrous toluene at 90 °C in the presence of dipolarophiles containing an activated C=C double bond gave rise to 1,3-dipolar adducts **18**−**27** in high yields (Table 1). When the reactions are performed under solvent-free conditions at 140 °C they proceed much faster with formation of the same products.

The structures of compounds **18**−**27** were verified by ^{1}H, ^{13}C, ^{1}H 2D NOESY NMR, IR spectroscopy, and elemental analysis. Structures of **19** and **20** were further confirmed by X-ray analysis (Figure 1). It was found that methanolysis of anhydride **22**, catalyzed by sulfuric acid, gives a compound identical to compound **19**, which is the product of reaction of aziridine **8a** with dimethyl maleate. As the configuration

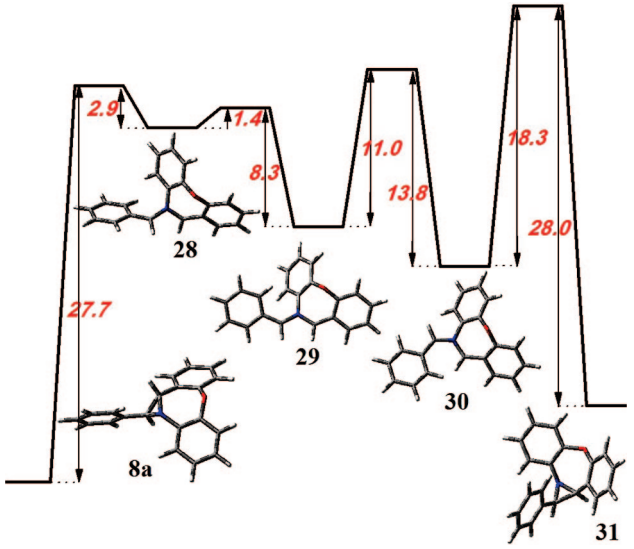


Figure 2. Reaction profiles for transformations of aziridines and ylides. Relative free energies (kcal•mol^{-1}, 298 K) computed at the B3LYP/6-31G(d) level.

of the stereocenters is preserved during the transformation of the anhydride to the ester in acidic conditions, the obtained result provides further evidence for the identical stereochemistry of compounds **19** and **22**.

It was shown that compounds **18**−**27** did not isomerize under the reaction conditions. ^{1}H NMR analysis of the reaction mixtures obtained after heating aziridines **8** with dipolarophiles **9**−**16** showed no other stereoisomers of compounds **18**−**27**. Thus, cycloaddition of ylides **17** to derivatives of butenedioic acids proceeds with complete stereoselectivity.

According to DFT B3LYP/6-31G(d) calculations (Figure 2), the ring opening of aziridine **8a** occurs conrotatory with the formation of the nonplanar W-ylide **28**. The latter can be converted to the practically plane and much lower energy W-ylide **29** by rotation of the Ph-ring through a ∼1.4 kcal•mol^{-1} activation barrier. Ylide **29** in turn can be transformed to an even more stable S-ylide **30** by rotating the PhCH group around the ylide C−N bond. The stereochemistry of cycloadducts **18**−**27** testifies to the participation of only the W-ylide in the cycloaddition. Furthermore, the cycloaddition of *cis*-dipolarophiles proceeds via the *exo*-transition state. One can also conclude from the results obtained that the observed stereoselectivity is apparently due to the lower barrier to cycloaddition of ylide **29** compared to the barrier to transformation of ylides **29** → **30**.

In summary, a novel effective approach to azirino-fused heterocycles was described. Thus, as an example, 1-aryl-1,11b-dihydoazirino[1,2-*d*]dibenz[*b*,*f*][1,4]oxazepines were synthesized by making use of the following domino sequence: isomerization of *gem*-dichloroaziridine−intramolecular Friedel−Crafts acylation of the *O*-tethered benzene ring and subsequent hydride induced intramolecular cyclization of the C-(arylchloromethyl)-substituted *C*═N unit. These oxazepines are excellent precursors of azomethine ylides which easily undergo completely stereospecific and stereoselective 1,3-dipolar cycloadditions to C═C dipolarophiles with the formation of derivatives of the new heterocyclic system−dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine. The cycloaddition is very effective in solvent free conditions. Further applications of the suggested methodology are currently under investigation.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds, CIF files for **8a**, **19**, and **20**, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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