New Application of Burgess Reagent in its Reaction with Epoxides

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We dedicate this paper to Ray Lemieux in recognition of his many contributions to organic synthesis.

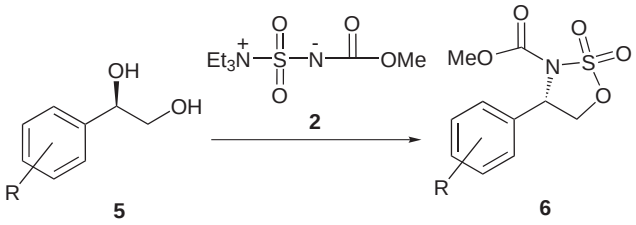
Abstract: Burgess reagent, (methoxycarbonylsulfamoyl)triethylammonium hydroxide, usually used for the dehydration of secondary or tertiary alcohols, was successfully employed in the formation of sulfamidates from the corresponding epoxides. It was further shown that the same reaction with aromatic epoxides results in the formation of seven-membered ring systems.

Key words: amino alcohols, Burgess reagent, epoxides, heterocycles, regioselectivity

In 1970 Burgess and coworkers described a new and very mild method for the dehydration of secondary and tertiary alcohols to the corresponding olefins using the inner salt of (methoxycarbonylsulfamoyl)triethylammonium hydroxide (**2**, Burgess reagent).[1] The proposed mechanism involves the attack of the hydroxyl functionality onto the sulfur followed by *syn*-elimination of the intermediate sulfamate (**3**), Scheme 1.

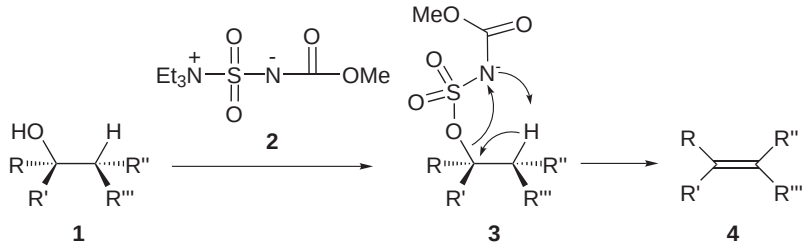
The Burgess reagent has been used primarily for the dehydration of secondary and tertiary alcohols,[2] and its use has figured in the total synthesis of important natural products, for example in Rigby's syntheses of narciclasine[3] and cedrene,[4] Nicolaou's synthesis of efrotomycin,[5] Uskokovic's synthesis of pravastatin,[6] and Holton's synthesis of Taxol®.[7] Further applications have been reported, for example nitrile formation from primary amides,[8] isocyanide formation from formamides,[9] and synthesis of urethanes from primary alcohols.[1,10] Wipf developed a polyethyleneglycol linked version of Burgess reagent and successfully employed it in the preparation of labile oxazolines.[11]

Recently Nicolaou and coworkers reported a novel application of Burgess reagent in the regio- and stereoselective synthesis of sulfamidates from 1,2-diols,[12] which can be further used in reactions with various O-, S-, N-, and C-nucleophiles.[13] This new approach is highly efficient and advantageous as the use of β-amino alcohols as starting material is not required. Nicolaou mainly concentrated on several styrene-derived diols (see Scheme 2). However, the reaction also proved to be successful with aliphatic compounds.



Scheme 2 Regio- and stereoselective synthesis of sulfamidates from several styrene-derived diols.

We became interested in the reaction of Burgess reagent with different diols and wanted to extend this methodology to synthetically more useful epoxides. Should such a reaction occur, it would provide a protocol for the synthesis of both *cis*- and *trans*-β-amino alcohols since the intermediate sulfamidate can be either reductively cleaved or transformed with inversion to *cis*-amino alcohols, as shown in Scheme 3. The latter process is analogous to the opening of cyclic sulfates with ammonium salts of car-



Scheme 1 Proposed reaction mechanism for the dehydration of alcohols with Burgess reagent.

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boxylic acids.[14,15] Furthermore, if such a scheme were successful, chiral versions of the Burgess reagent could be constructed for the asymmetric opening of *meso* epoxides.

At least one case is known in which a compound containing a hydroxyl functionality and an epoxide was allowed to react with Burgess reagent leaving the epoxide moiety intact.[16] This example led to a statement contained in a recent review:

'The compatibility of the Burgess reagent with many functionalities, e.g. *halogens, epoxides, alkenes, alkynes, aldehydes, ketones, acetals, esters, secondary amides, makes it an attractive technique for the introduction of C-C double bonds into highly functionalized molecules.'*[2b]

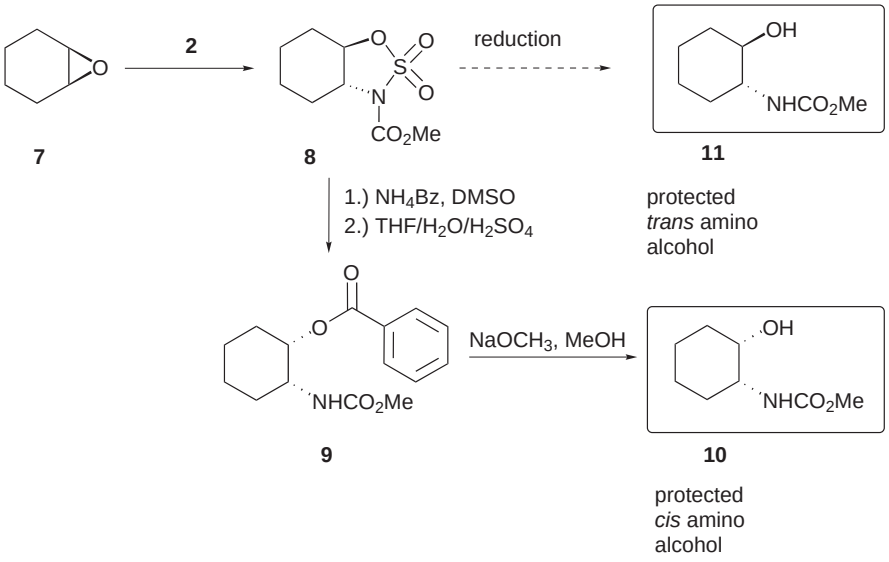
Cyclohexene oxide (**7**) was chosen as the simplest model to test and optimize the reaction, and we found that its treatment with the Burgess reagent resulted in the formation of the desired sulfamidate **8**. In a comparison of eight solvents (DMF, DME, THF, Et_2O, CH_2Cl_2, C_6H_6, DMSO, and HMPA), it was found that ethers (DME, THF or Et_2O) were best for the formation of the sulfamidate, but product formation was also observed in CH_2Cl_2. Best results in regard to yield were obtained when the reaction was carried out in either DME or THF at temperatures between 50 °C and 70 °C for a reaction time of 1.5 hours with an excess of Burgess reagent (2.3 equiv).

Nucleophilic opening of the sulfamidate **8** (see Scheme 3) afforded benzoate **9**, which is easily transformed into protected amino alcohol **10**. This is an interesting result as it provides access to *cis*-amino alcohols from epoxides with double inversion of configuration. Reduction of the sulfamidate would provide the *trans* isomer **11**; conditions for this reduction have not been found as of this writing and several methods tried (Na/NH_3, Na/naphthalene, Na/anthracene) did not reduce the sulfamidate.

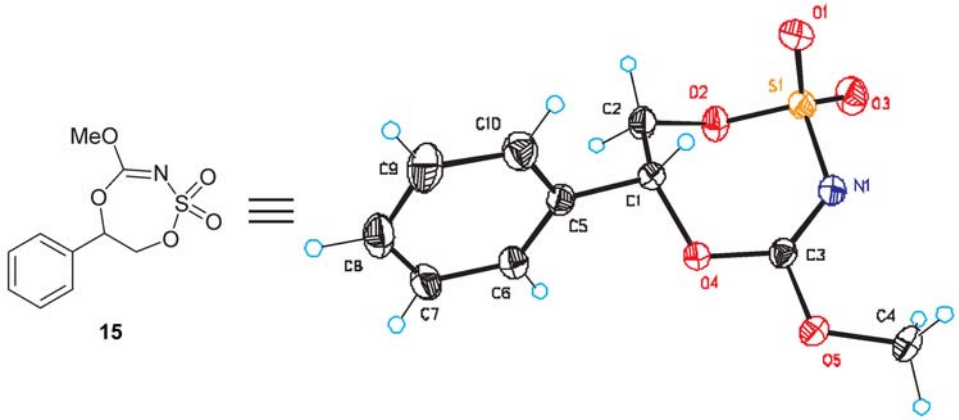
When the reaction was carried out with 1,2-epoxyhexane under conditions described above (THF, 2.3 equiv of Burgess reagent, 1.5 hours at 50 °C), formation of the expected sulfamidate was observed. The product obtained from this reaction was found to have the same regiochemistry as the product from the corresponding reaction with 1,2-hexanediol.

An interesting observation was made when styrene oxide (**14**) and naphthalene oxide (**17**) were allowed to react with Burgess reagent under the same reaction conditions as those used for the aliphatic epoxides. The expected products **16** and **19** were formed in very small quantities. The major products formed in these reactions were initially thought to be regioisomers that were assigned by Nicolaou on the basis of an analogy with an x-ray of a similar compound.[12] The IR data of the product did not match the structure proposed by Nicolaou and coworkers.[17] The required carbonyl signal for the carbamate was missing and a band at 1603 cm^{-1} suggested the presence of a C=N double bond. Furthermore, results from long-range coupling experiments (HMQC) showed that the carbon from the C=N double bond was coupled to the proton at the benzylic position. The structure was finally assigned by acquiring an x-ray crystal structure as **15** (Scheme 4).

Examination of the ^1H NMR spectrum (kindly provided by Prof. Nicolaou) of the crude reaction mixture of styrene diol (**20**) with the Burgess reagent, revealed that the signals for the minor product, assumed to be '**16b**', matched the ^1H NMR of **15** obtained from the reaction with styrene oxide (see Scheme 5). It was also clear that the data provided for the proposed and published structure **16b**[12] were identical to the data for the major product observed by us from the reaction with epoxides. We attempted to unambiguously prove the regiochemistry of '**16b**' by exhaustive hydrolysis under conditions reported by Bergmeier[18] (Dowex 1 × 8–100 ion exchange resin). If **16b** had the proposed structure, we should have obtained the corresponding amino alcohol, a known compound. Incredibly, we obtained a moderate yield of styrene oxide!



Scheme 3 Reaction of Burgess reagent with cyclohexene oxide and transformation of the product into protected cis-aminoalcohol **10**.



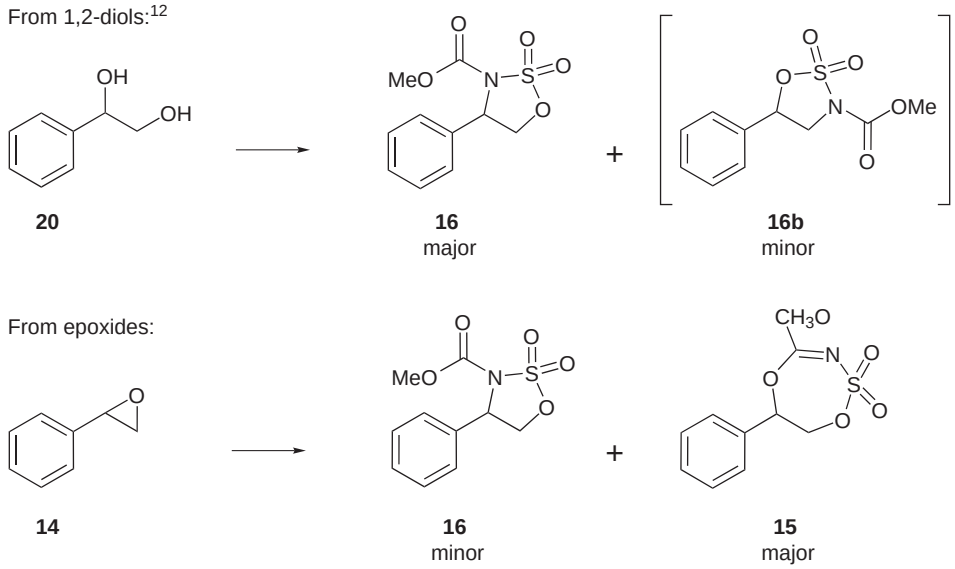
Scheme 4 X-ray crystal structure of **15**.[21]

There is essentially no rational way to convert **16b** to styrene oxide under basic conditions; however, such pathway is possible from **15** (confirmed by x-ray) as outlined in Scheme 6.

The formation of the seven-membered ring system can be explained by assuming that the resonance hybrid (**2a**) of Burgess reagent is involved in the reaction (see Scheme 6). The same observation was made when naphthalene oxide was allowed to react with Burgess reagent. Instead of the five-membered ring system, the corresponding seven-memebered ring was formed as the major product. Interestingly, the resonance hybrid **2a** only plays a role in the reaction with epoxides at benzylic position. In addition, when a known amount of styrene oxide was added to the reaction of the Burgess reagent with styrene diol the amount of epoxide-derived product increased significantly (Table 1, entry 6). In an analogous experiment where a known amount of styrene diol was added to the reaction of the Burgess reagent with styrene oxide, the amount of diol-derived product increased in a similar fashion (Table 1, entry 5). A plausible rationalization of these observations is portrayed in Scheme 6.

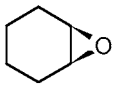
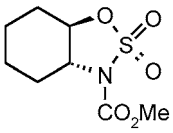
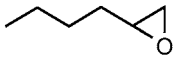
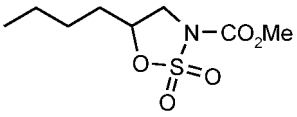
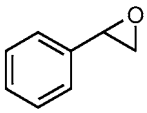
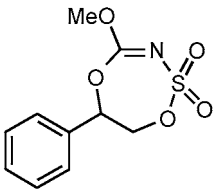
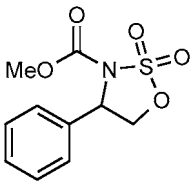
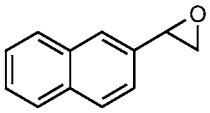
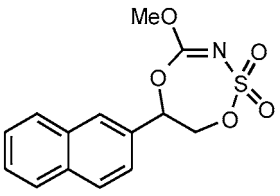
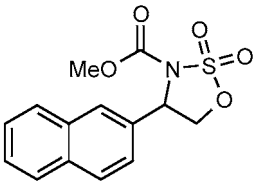
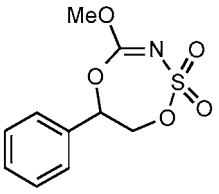
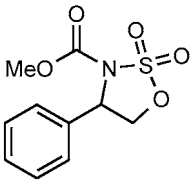
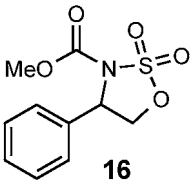
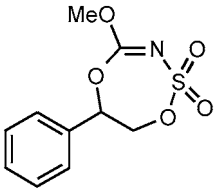
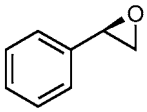
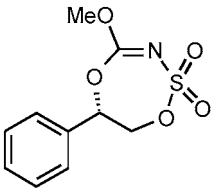
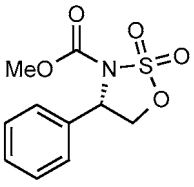
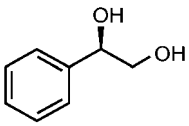
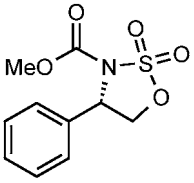
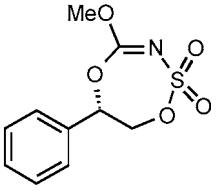
It is likely that under the conditions of the reaction with diols reported by Nicolaou approximately 10% of the intermediate **21** suffers internal deprotonation to generate **22**, which in turn generates styrene oxide whose reaction with Burgess reagent proceeds via resonance hybrid **2a** to form **15**. This proposed mechanistic pathway was partially supported by the reaction of Burgess reagent with optically pure styrene oxide **26** and optically pure styrene diol **29**. Both reactions yielded the same enantiomer of **27**, as the major product from epoxide and a minor product from the diol ($[\alpha]_D^{20}$ –43, *c* 1.0, $CHCl_3$), Table 1. Hydrolysis of sulfamidate **27** under basic conditions[18] (LiOH, dioxane–water) yielded styrene diol with the opposite configuration as the starting diol **29**.

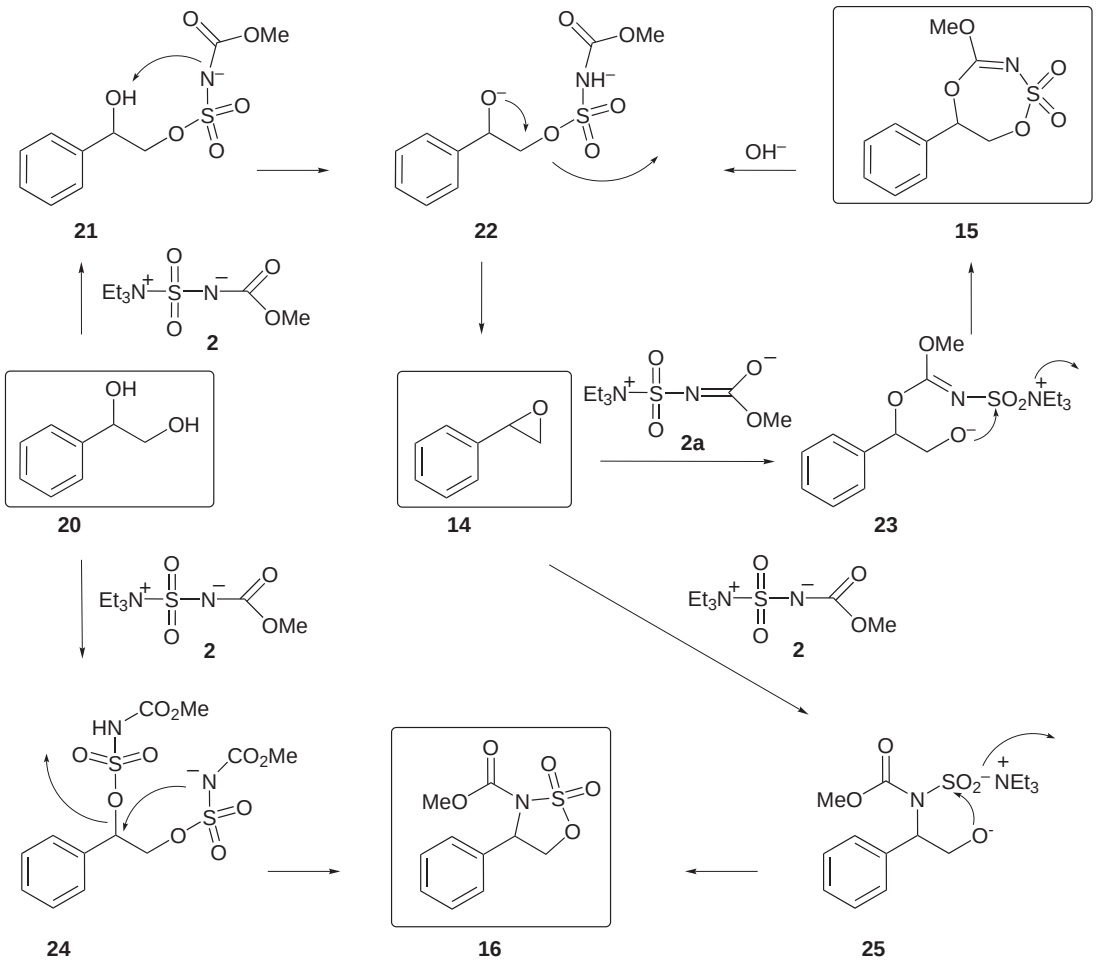
In light of the above experiments it seems likely that the other minor products reported by Nicolaou for the reactions of the Burgess reagent with various diols may also be the seven-membered sulfamidates. Results of the reaction of aliphatic and aromatic epoxides with Burgess reagent are summarized in Table 1 (for ^{1}H NMR data of all new compounds see ref.[19]).



Scheme 5 Comparison of the reaction of Burgess reagent with styrene diol[12] and styrene oxide.

Table 1 Reaction of Epoxides with the Burgess Reagent

Entry	Starting material	Major product	Minor product	Ratio	Total yield [%]
1	 **7**	 **8**	–	–	64
2	 **12**	 **13**	–	–	68
3	 **14**	 **15**	 **16**	92:8	72
4	 **17**	 **18**	 **19**	90:10	70
5	**14** (1.0 equiv), **20** (0.2 equiv) (added 1 min after reaction started)	 **15**	 **16**	80:20	65
6	**20** (1.0 equiv), **14** (0.2 equiv) (added 1 min after reaction started)	 **16**	 **15**	77:23	55
7	 **26**	 **27**	 **28**	91:9	66
8	 **29**	 **28**	 **27**	90:10	56



Scheme 6 Difference in the reactivity of Burgess reagent with styrene oxide and styrene diol.

In conclusion we have shown that Burgess reagent can be used in the reaction with epoxides to generate synthetically useful sulfamidates and to provide a potential for the synthesis of both *cis* and *trans* amino alcohols from the same diastereomer of an epoxide. Furthermore, the difference in reactivity between aromatic and aliphatic epoxides is interesting from a mechanistic point of view and continues to be the focus of our current investigations along with investigations directed at the asymmetric version of the reagent.[20]

To a solution of 480 mg styrene oxide **14** (4.0 mmol) in 20 mL of THF at 70 °C was added 2.38 g of Burgess reagent (9.2 mmol) **2**. The reaction mixture was stirred at 70 °C for 1.5 hours before the solution was filtered through a plug of silica. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using a mixture of hexanes–ethyl acetate (5:1) as eluent affording 670 mg of **15** (66%).

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(17) We thank Professor K. C. Nicolaou for providing the NMR/IR data for **16** and **19**.
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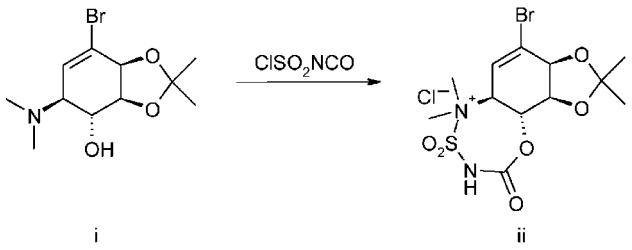
(19) All NMR data were obtained on a Varian 300 MHz instrument and chemical shifts are reported in ppm in respect to TMS (0 ppm). **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.00 (m, 1 H), 4.22 (m, 1 H), 3.90 (s, 3 H), 2.33 (m, 2 H), 1.45–1.85 (m, 5 H), 1.16–1.33 (m, 2 H); **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (m, 1 H), 4.15 (dd, *J* = 9.7 Hz, 5.6 Hz, 1 H), 3.84 (s, 3 H), 3.66 (t, *J* = 9.7 Hz), 1.81–1.95 (m, 1 H), 1.65–1.78 (m, 1 H), 1.25–1.45 (m, 4 H), 0.87 (t, *J* = 6.7 Hz, 3 H); **15**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.47 (m, 5 H), 6.15 (dd, *J* = 10.7 Hz, 3.6 Hz, 1 H), 4.62 (dd, *J* = 12.6 Hz, 10.5 Hz, 1 H), 4.52 (dd, *J* = 12.6 Hz, 3.6 Hz, 1 H), 3.93 (s, 3 H); **18**: ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.85–7.91 (m, 4 H), 7.43–7.60 (m, 3 H), 6.32 (dd, *J* = 10.8 Hz, 3.3 Hz, 1 H), 4.73 (dd, *J* = 12.9 Hz, 11.1 Hz, 1 H), 4.61 (dd, *J* = 12.3 Hz, 3.6 Hz, 1 H), 3.96 (s, 3 H).
(20) Homochiral aminoalcohol **i** has been used to prepare the bicyclic derivative **ii**, conversion of **ii** to the asymmetric version of the Burgess reagent and its reactions with meso and racemic epoxides are under investigation (Scheme 7).



i ii

Scheme 7

(21) All queries regarding X-ray data should be directed to Khalil A. Abboud. E-mail: abboud@chem.ufl.edu