solution to an excess of precooled sodium methoxide in methanol. The colorless mixture was allowed to warm to room temperature, then diluted with water, and extracted with pentane. The organic extract was washed ($NaHCO_3$, NaCl), dried, and evaporated in a stream of nitrogen to give a colorless oil. ^1H NMR showed the product to be predominantly a single compound, **1-methyl-*endo*-4-methoxytricyclo[3.3.0.0^{2,8}]octane (11b, X = OCH$_3$).** ^1H NMR (400 MHz): δ 3.83 (dt, J = 8.8, 6.0 Hz, H_{4ex}), 3.21 (s, 3 H, OCH_3), 2.28 (m, 2 H), 1.98 (ddd, J = 3.0, 6.0, 13.2 Hz, H_5), 1.70 (m, 1 H), 1.45 (m, 1 H), 1.30 (s, 3 H, CH_3), 1.10–1.25 (m, 2 H), 0.80–0.95 (m, 2 H, $H_{2,8}$). ^{13}C NMR, see Table II. MS (E.I., 70 eV): m/z (relative intensity) 152 ($M^{+\bullet}$, 25), 120 (17), 105 (15), 94 (49), 91 (24), 81 (52), 79 (77), 77 (25), 71 (100); M^+ calcd 152.1201, obsd 152.1167.

6a-Methylhexahydro-2,6-methano-2*H*-cyclopenta[*b*]furanium (22). Addition of syn alcohol **9b** (X = OH) (100 mg, 0.72 mol) to FSO_3H/SO_2ClF at −78 °C gave a clear orange solution (0.36 M). ^{13}C NMR (25 MHz, −90 °C): 116.0 (s, C_{6a}), 94.1 (d, J = 173 Hz, C_2), 43.3 (d, J = 149 Hz, $C_{6,3a}$), 39.9 (t, J = 138 Hz, $C_{3,7}$), 27.4 (t, J = 134 Hz, $C_{4,5}$), 16.2 ppm (q, J = 133 Hz, CH_3). Addition of the ion solution to excess precooled sodium methoxide/methanol as above followed by similar workup yielded a pale yellow oil (90 mg). Preparative GLC yielded the two components identified as **21** (identical with authentic material) and **18** (1:9).

6a-Methylhexahydro-2,6-methano-2*H*-cyclopenta[*b*]furan (18). IR (film): 2942, 2868, 1380, 1131, 878 cm^{-1}. ^1H NMR (400 MHz): δ 4.33 (t, $J_{2,3ex}$ = 5 Hz, 1 H, H_2), 2.13 (m, $J_{3ex,3en}$ = 12 Hz, $J_{3ex,3a}$ = 10.5 Hz, $J_{3ex,2}$ = 5 Hz, 2 H, H_{3ex}), 1.87 (m, 4 H, H_{3a}, H_{4ex}), 1.65 (~d, J = 7.5 Hz, 2 H, H_{4en}), 1.43 (s, 3 H, CH_3), 1.22 (~d, J = 12 Hz, 2 H, H_{3en}). ^{13}C NMR, see Table II. MS (EI, 15 eV): m/z (relative intensity) 138 ($M^{+\bullet}$, 43), 95 (30), 94 (100), 88 (6), 86 (42), 84 (65), 80 (13), 71 (27), 68 (12), 43 (4); M^+ calcd 138.1044, obsd 138.1058. Anal. Calcd for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 78.60; H, 10.04.

Acknowledgment. We thank Professors R. M. Coates of the University of Illinois and P. G. Gassman of the University of Minnesota for samples of **25** and **13**, respectively, and for reading the manuscript, Dr. T. M. Ford for preparation of the tricyclooctyl chlorides **8** and **11**, Mr. S. K. Danek for one sample of the anti alcohol **8b**, Ms. V. Stokie for synthesis of **21**, Ms. W. A. Jensen for her contribution to the work on methylcyclohexyl cations, Dr. D. Brecknell of University of Queensland for a sample of 1,4-cineole, Ms. K. Karavokiros for preparation of 2-bicyclo[2.2.2]octanone, and Dr. J. M. Shooley of VARIAN for NMR data of 5,5-dimethylbicyclo[2.1.1]hexan-2-one. J.J.G. and D.R.L. acknowledge receipt of Commonwealth Postgraduate Awards. The hospitality of Professor H. C. Brown at Purdue University is gratefully acknowledged by D.P.K. The work was supported by the Australian Research Grants Committee.

Registry No. **3**, 1755-04-0; **5**, 59856-43-8; **6b** (X = OH), 87969-57-1; **7**, 5164-64-7; **8b** (X = OH), 83198-89-4; **8b** (X = OCH_3), 113894-45-4; **9b** (X = OH), 38310-50-8; **9b** (X = OCH_3), 113974-20-2; **11b** (X = OCH_3), 38310-54-2; **12**, 51900-16-4; **13**, 14224-86-3; **14**, 113892-33-4; **18**, 106200-60-6; **19**, 470-67-7; **20**, 70837-34-2; **21**, 65461-12-3; **22**, 113894-48-7; **24b** (X = OCH_3), 55794-07-5; **25**, 20682-66-0; cyclopentanone, 120-92-3; pyrrolidine, 123-75-1; 1-(1-cyclopenten-1-yl)pyrrolidine, 7148-07-4; *exo*-2-(*N*-pyrrolidinyl)bicyclo[3.2.1]octan-8-one, 113894-47-6; *endo*-2-(*N*-pyrrolidinyl)bicyclo[3.2.1]octan-8-one, 113894-46-5; 4-cycloheptene-1-carboxylic acid, 1614-73-9.

Computer-Assisted Mechanistic Evaluation of Organic Reactions. 15. Heterocycle Synthesis

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CAMEO, an interactive computer program that predicts the products of organic reactions primarily through applying generalized rules governing reactivity, has been expanded to treat the major types of heterocycle-forming reactions, i.e., addition and substitution reactions under neutral and acidic conditions. Furthermore, syntheses involving base-catalyzed and pericyclic reactions, electrophilic aromatic substitution, and radical or carbenoid intermediates are handled via a mechanistic selection algorithm. This permits thorough coverage of the preparation of three- through eight-membered aromatic and nonaromatic heterocycles with one or more N, O, or S atom. Key considerations in the processing include determination of mechanistic type, classification of nucleophilic and electrophilic sites, and assessment of selectivity. A novel facet of the treatment is the construction of intermediates and products using a method that features "heterocyclic extended mechanistic steps". The study begins with a brief overview of the fundamental aspects of heterocycle-forming reactions. A discussion of the implementation of this module in CAMEO follows including sample reaction sequences predicted by the program.

I. Introduction

CAMEO is an interactive computer program that predicts the products of organic reactions given starting materials and reaction conditions. The program arrives at its predictions mainly through the use of mechanistic reasoning rather than through brute force recall of reaction precedents. Accordingly, development of CAMEO entails the formulation of general rules governing reactivity for different classes of organic reactions. Currently, the program can evaluate base-catalyzed and nucleophilic,[1] acid-catalyzed and electrophilic,[2] electrophilic aromatic substitution,[3] pericyclic,[4] oxidative,[5] and reductive[6] reactions. In addition, treatment of reactions involving radical, carbene, and nitrene intermediates is being implemented.

The program has also been expanded to include comprehensive coverage of reactions used in the synthesis of heterocyclic compounds as described here. This addition has much enhanced the program's capabilities for analyzing synthetic routes to biologically important molecules.

(1) Salatin, T. D.; Jorgensen, W. L. *J. Org. Chem.* **1980**, *45*, 2043. Salatin, T. D.; McLaughlin, D.; Jorgensen, W. L. *J. Org. Chem.* **1981**, *46*, 5284. Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 1056. Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1986**, *51*, 3513. Metivier, P.; Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1987**, *52*, 3724. Gushurst, A. J.; Jorgensen, W. L., in press.

(2) McLaughlin, D. R. Ph.D. Thesis, 1983, Purdue University.

(3) Bures, M. G.; Roos-Kozel, B. L.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 4490.

(4) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923. Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001.

(5) Paderes, G. Ph.D. Thesis, 1988, Purdue University.

(6) Metivier, P.; Jorgensen, W. L., manuscript under preparation.

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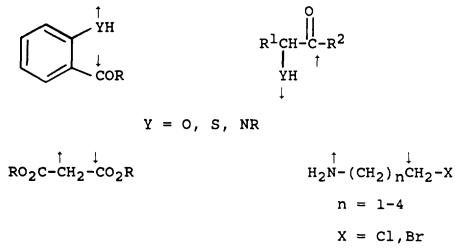


Figure 1. Examples of reactants containing electrophilic and nucleophilic centers. (↑ is nucleophilic center and ↓ is electrophilic center).

Naturally, identification and evaluation of the key factors determining reactivity for this class of processes has been required. Thus, algorithms were developed to deal with the assignment of mechanistic type, identification and classification of nucleophiles and electrophiles, and selectivity. In addition, a novel method of constructing intermediates and products of heterocycle-forming reactions, featuring "heterocyclic extended mechanistic steps", has been developed. The paper opens with a brief overview of the major aspects of heterocycle synthesis followed by a discussion of the implementation of this module in CAMEO. To conclude, sample reaction sequences predicted by the program are analyzed.

II. Key Aspects of Heterocycle Synthesis

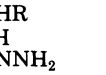
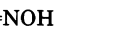
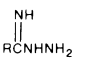
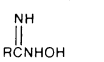
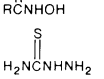
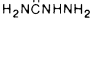
For over a century the development of general and efficient methods of heterocycle synthesis has been a major area of research. Thus, several excellent monographs are available, e.g., Paquette (1968),[7] Joule and Smith (1978),[8] Newkome and Paudler (1982),[9] Katritzky (1985),[10] and Gilchrist (1985).[11] In this section an overview of the principal methods of forming heterocycles is presented. The intent here is to indicate the scope of the chemistry, some of the most important reactions, and how they can be organized. In-depth treatments for specific reactions or mechanistic types are available in the numerous references that are cited.

The majority of heterocycle syntheses involve ring-forming reactions of open-chain precursors. The general methods of forming heterocycles have been divided into two broad categories, cyclization and cycloaddition reactions.[11] Cyclization methods utilize most of the ordinary σ-bond-forming processes, i.e., nucleophilic, electrophilic, radical, carbene, and nitrene reactions and proceed in a step-wise manner. However, cycloadditions feature synchronous formation of two bonds as in 1,3-dipolar cycloadditions, Diels–Alder reactions, and [2 + 2] cycloadditions. The two categories of reactions are expanded on in the following.

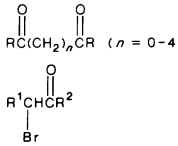
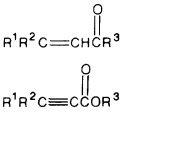
A. Cyclization Processes. 1. Nucleophilic and Electrophilic Reactions. Reactions involving the combining of a nucleophile and an electrophile comprise the most common type of heterocycle synthesis. A convenient way to classify these reactions is according to the nature of the components involved. Specifically, reactions can occur between a reactant with two nucleophilic centers (binucleophile) and a substrate with two electrophilic sites

Table I. Examples of Binucleophiles and Bielectrophiles

A. Binucleophiles[a]

1,2-systems	1,3-systems	1,4-systems
RNHNHR		$H_2N(CH_2)_2NH_2$
RNHOH		$H_2N(CH_2)_2OH$
$RCH{=}NNH_2$		
RCH=NOH		
		
		
		
		

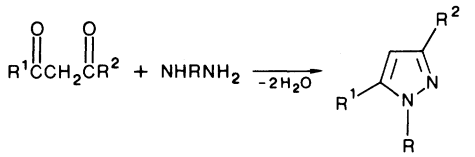
B. Bielectrophiles

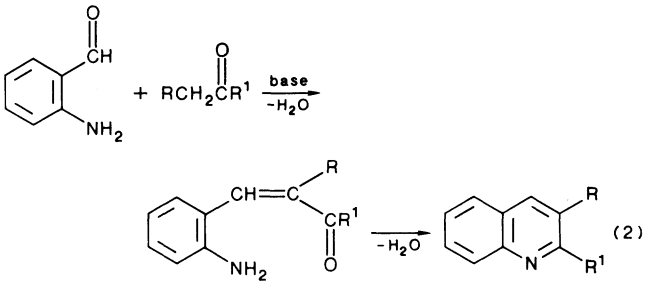
$(RO)_2C{=}O$ $Cl_2C{=}X$ (X = O, S, NR)

[a] Adapted from ref 10, p 382.

(bielectrophile). A classic example of this type is the reaction of diketones with hydrazines, as in the formation of pyrazoles (eq 1[11]). Other representative binucleophiles


(1)

and bielectrophiles are presented in Table I. An alternate approach is the reaction of two compounds in which one or both contains an electrophilic and a nucleophilic center (e.g., Figure 1). The Friedlander quinoline synthesis (eq 2[11]) is an example of this type of reaction. A final method


(2)

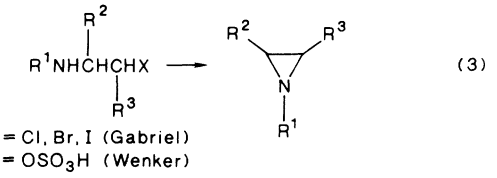
is the intramolecular cyclization of a reactant that is equipped with both an electrophilic and nucleophilic site, as presented in sections a–c below.

The major mechanistic types for nucleophilic and electrophilic formation of heterocycles are (a) S_N2, (b) addition, (c) addition–elimination, and (d) electrophilic aromatic substitution. These classes are discussed in the following sections with emphasis on reactivity, scope, and application.

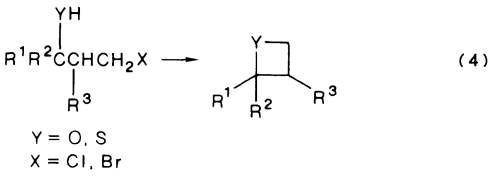
a. S_N2. Although the construction of heterocycles with ring sizes varying from 3 to ca. 20 is possible, the S_N2 approach is especially useful for three- and four-membered rings.[11-14] Classic examples are the Gabriel and Wenker

(7) Paquette, L. A. *Principles of Modern Heterocyclic Chemistry*; Benjamin: New York, 1968.
(8) Joule, J. A.; Smith, G. F. *Heterocyclic Chemistry*, 2nd ed.; VanNostrand Reinhold: New York, 1978.
(9) Newkome, G. R.; Paudler, W. W. *Contemporary Heterocyclic Chemistry*; Wiley: New York, 1982.
(10) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: Oxford, 1985.
(11) Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman: London, 1985.
(12) Deyrup, J. A. In *Small Ring Heterocycles*, Part 1; Hassner, A., Ed.; Wiley-Interscience: New York, 1983; p 11.
(13) Heine, H. W. In *Small Ring Heterocycles*, Part 2; Hassner, A., Ed.; Wiley-Interscience: New York, 1983; p 552.

syntheses of aziridines (e.g., eq 3[12]) and the formation of thietanes and oxetanes from β-halo alcohols and β-halo thiols, respectively (e.g., eq 4[11]).

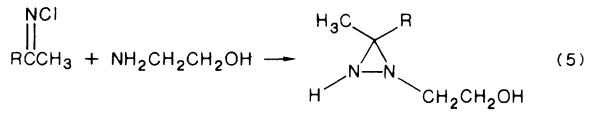


(3)



(4)

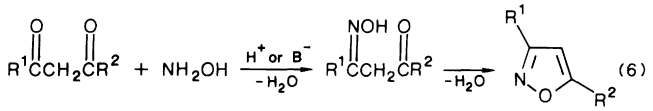
The above examples of intramolecular S_N2 reactions involve substitution at a saturated carbon atom. An alternate route to three- and four-membered heterocycles is intramolecular displacement at a heteroatom equipped with a good leaving group. This process is illustrated in eq 5.[13]



(5)

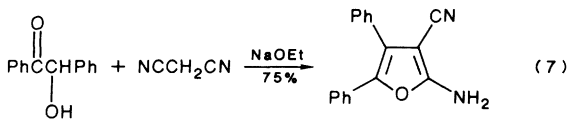
A key factor influencing the rate of intramolecular cyclization is the size of the ring formed. Closure to five- and six-membered rings generally proceeds at the greatest rate. Three-membered heterocyclic ring formation under basic conditions is also a facile process. Some quantitative data on the effect of incipient ring size on the relative rates of two intramolecular cyclizations are given in Table II.

b. Addition. The most extensively used reaction in heterocycle synthesis is addition to carbonyl compounds. Addition reactions are especially useful for the preparation of five- and six-membered heteroaromatic rings. A common approach involves intermolecular addition of a nucleophilic heteroatom to a dicarbonyl species to form an acyclic intermediate. This intermediate then cyclizes via an intramolecular addition to form a heterocycle. The process is exemplified by the formation of isoxazoles from 1,3-dicarbonyl compounds and hydroxyl amine (e.g., eq 6[11]). Note that addition to carbonyl groups is usually followed by dehydration, especially when this results in the formation of a heteroaromatic ring.



(6)

Addition reactions can be performed in neutral, basic, or acidic media. Base-catalyzed reactions typically involve active methylene compounds, as in eq 7.[15] Under these



(7)

conditions, an anion is the key reactive species and the reactions are deemed nucleophilic. Neutral or acidic conditions are most often used for reactions involving

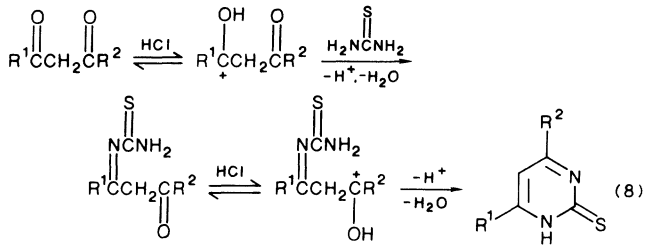
(14) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(15) Taylor, E. C.; McKillop, A. *Adv. Org. Chem.* **1970**, *7*, 127.

Table II. Effect of Ring Size on Relative Rates of Intramolecular Heterocycle-Forming Cyclizations

ring size (n)	rel rate
Cyclization of Bromoalkylamines $Br(CH_2)_{n-1}NH_2$ (Water, 25 °C)[a]	
3	6.7×10^1
4	1
5	6×10^4
6	1×10^3
7[b]	6.6×10^1
Cyclization of Chloroalkoxides $Cl(CH_2)_{n-1}O^-$ (30 °C)[a]	
3[c]	5.3×10^3
4	1
5	2.8×10^4
6	1.3×10^2

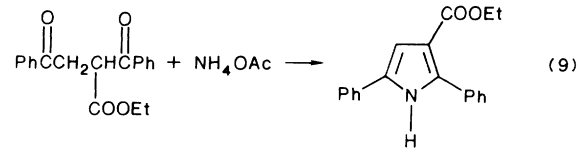
[a] Data adapted from ref 14. [b] Reaction temperature was 73 °C. [c] Reaction temperature was 25 °C.

nucleophilic heteroatoms. Under acidic conditions attack of the heteronucleophile is facilitated by protonation of the electrophilic group (e.g., eq 8[11]). Since a cationic

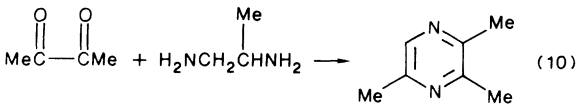


(8)

species is involved, these reactions are deemed electrophilic. Some additional examples of heterocycle syntheses via electrophilic addition reactions are the Knorr pyrrole synthesis (e.g., eq 9[16]) and the condensation of diamines with 1,2-diones to form pyrazines (e.g., eq 10[17]).



(9)

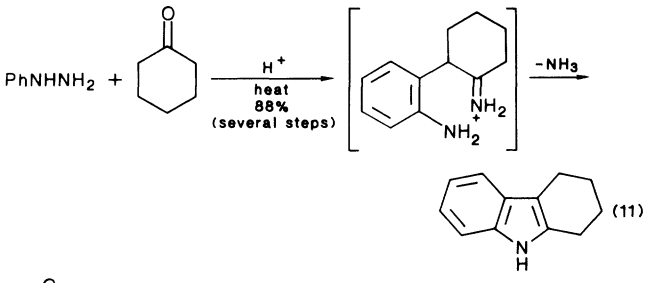


(10)

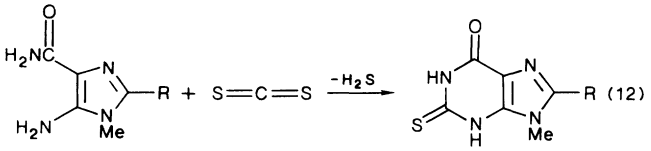
Addition to double bonds other than carbonyl groups is another important route to heterocycles. Addition to imines or thiones followed by loss of ammonia or hydrogen sulfide, respectively, has been used as a route to heteroaromatic ring systems. For example, the last step of the Fischer indole synthesis features addition to an iminium group (e.g., eq. 11[18]), while addition to a carbon–sulfur double bond usually involves activated electrophiles as illustrated in eq 12.[19]

Though the previous examples in this section have all involved addition to double bonds, addition to triple bonds is also a useful method of forming five- and six-membered heterocycles. For example, addition to nitriles provides a widely used route to amino-substituted heterocycles (e.g., eq 13[20]).

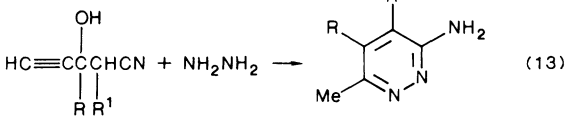
(16) Spiro, V.; Fabra, J. *Ann. Chim. (Paris)* **1960**, *50*, 1635.
(17) Marion, J. P. *Chimia* **1967**, *21*, 510.
(18) Rogers, C. U.; Corson, B. B. *J. Am. Chem. Soc.* **1947**, *69*, 2910.
(19) Cook, A. H.; Smith, E. *J. Chem. Soc.* **1949**, 2329.
(20) Golodova, K. G.; Yakimovich, S. I.; Perveev, F. Ya. *Zh. Org. Khim.* **1972**, *8*, 2488.



(11)



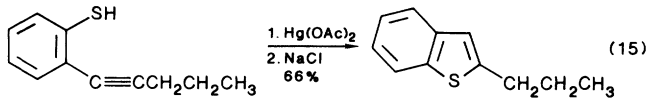
(12)



(13)

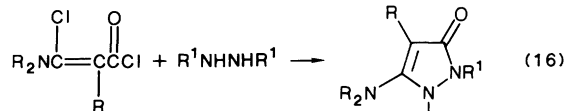
Furthermore, a newer method of synthesizing some five- and six-membered heterocycles involves addition to carbon–carbon triple bonds. Cyclization in an exo fashion can lead to alkyl-substituted heterocycles (e.g., eq 14[21]), while endo cyclization has also been observed as exemplified in eq 15.[22]

(14)



(15)

c. Addition–Elimination. Addition to esters, acid halides, thionyl halides, etc., is another common route to five- and six-membered heterocyclic compounds. With these electrophiles, addition is followed by loss of a leaving group. Therefore, heterocycles which contain exo C=X (X = O, S, NR) bonds are typically produced unless a tautomerization or second addition/elimination occurs. Representative examples are depicted in eq 16[23] and 17.[24]



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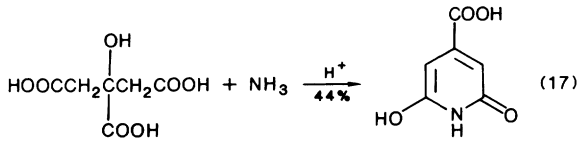
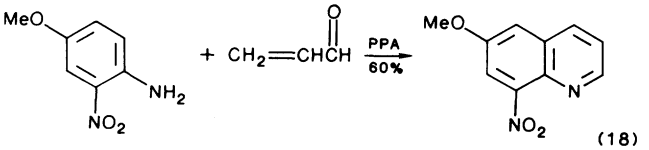


(17)

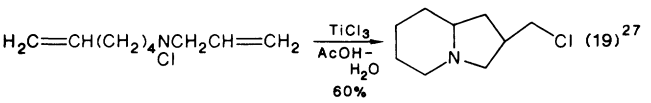
d. Electrophilic Aromatic Substitution. Intramolecular aromatic substitution is a useful method for forming benzo-fused heterocycles. The most common reaction partners are a heteroatom-substituted benzenoid compound and a bielectrophile. Attack at one electrophilic center of the bielectrophile is followed by electrophilic aromatic substitution with the second site. A classic example is the Skraup quinoline synthesis (e.g., eq 18[25]).



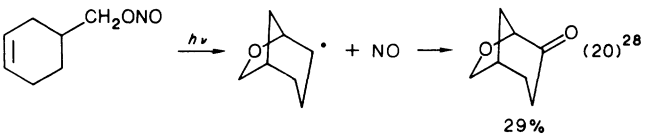
(18)

A wide variety of electrophiles participate in cyclization reactions to form benzo-fused heterocycles such as alkyl halides, ethers, acids, esters, and acid halides. These reactions are usually performed in the presence of a protic or Lewis acid catalyst. Under these conditions cyclization is often followed by dehydration to form the benzo-fused heteroaromatic compound.

2. Radical Cyclizations.[26] Intramolecular addition reactions of radicals have been used in the synthesis of saturated five- and six-membered heterocycles. One of the most useful radical cyclizations involves the reaction of a heteroatom radical with a double bond. This process can be used to form nitrogen-, oxygen-, and sulfur-containing heterocycles, e.g., eq 19–21.



(19)[27]



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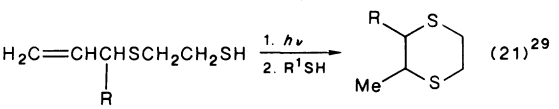
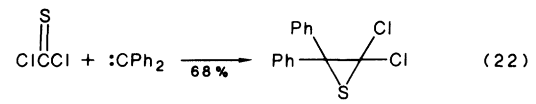
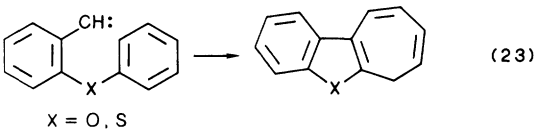


(21)[29]

3. Carbene[30] and Nitrene[31] Cyclizations. The characteristic reactions of carbenes and nitrenes are addition to multiple bonds and insertion into carbon–hydrogen bonds. Intermolecular and intramolecular versions of these reactions have been used to synthesize heterocycles as in eq 22[32] and 23.[33] A wide variety of alkyl, aryl, and

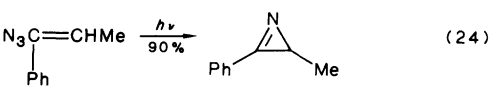


(22)



(23)

vinyl azides also participate in reactions which form heterocycles, as illustrated in eq 24.[34]

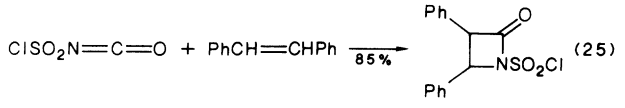


(24)

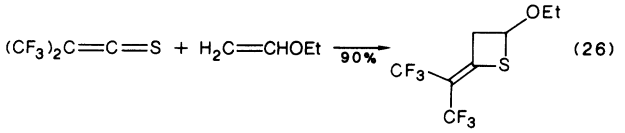
(21) deJong, A. J.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 15.
(22) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*. 4218.
(23) Reference 10, p 417.
(24) Bazier, R.; Dub, G.; Gister, C.; Steinberg, H. *J. Am. Pharm. Assoc.* **1956**, *45*, 478.
(25) Yale, H. L. *J. Am. Chem. Soc.* **1947**, *69*, 1230.
(26) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*, Vol. 1; Academic Press: New York, 1980; p 182.
(27) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337.
(28) Nouguier, R.; Surzur, J.-M. *Bull. Soc. Chim. Fr.* **1973**, 2399.
(29) Crozet, M.-P.; Surzur, J.-M. *Tetrahedron Lett.* **1971**, 2031.
(30) Kirmse, W. *Carbene Chemistry*; Academic Press: New York, 1971.
(31) Scriven, E. F. V., Ed. *Azides and Nitrenes*; Academic Press: Orlando, 1984.
(32) Staudinger, H.; Siegwart, J. *Helv. Chim. Acta* **1920**, *3*, 833, 840.
(33) Reference 10, p 489.

B. Cycloaddition Processes. Most of the traditional methods used to synthesize heterocycles involve cyclization reactions; however, application of cycloaddition methodology is expanding. A key reason for this growth is that cycloadditions can generate highly functionalized heterocycles with good regiochemical and stereochemical control. Cycloaddition reactions are especially useful for the preparation of four-, five-, and six-membered heterocyclic compounds. The most important reaction types are [2 + 2] cycloadditions, hetero-Diels–Alder reactions, and 1,3-dipolar cycloadditions.

1. [2 + 2] Cycloadditions.[35] A variety of four-membered heterocyclic rings with one or two heteroatoms can be formed by [2 + 2] cycloaddition. This method is a particularly useful route to β-lactams and other four-membered heterocyclic rings with exo double bonds. Compounds which participate in [2 + 2] cycloadditions include ketenes and heterocumulenes such as isocyanates, isothiocyanates, and carbodiimides. Typical reaction partners for these substrates are alkenes, enamines, and enol ethers. Representative examples are presented in eq 25[36] and 26.[37]

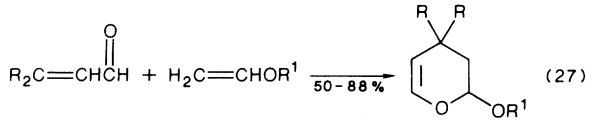


(25)



(26)

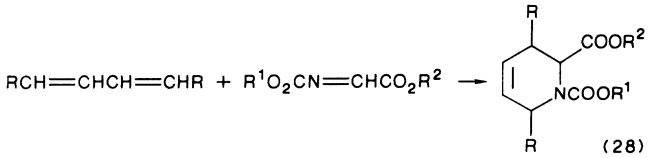
2. Hetero-Diels–Alder Reactions.[38,39] The use of [4 + 2] cycloadditions is increasing for syntheses of five- and six-membered heterocycles with one or two heteroatoms. These reactions can be classified according to the types of components involved. One approach is via the reaction of a heterodiene and a dienophile. A common example of this process is the formation of pyrans from α,β-unsaturated aldehydes and enol ethers (e.g., eq 27[40]).



(27)

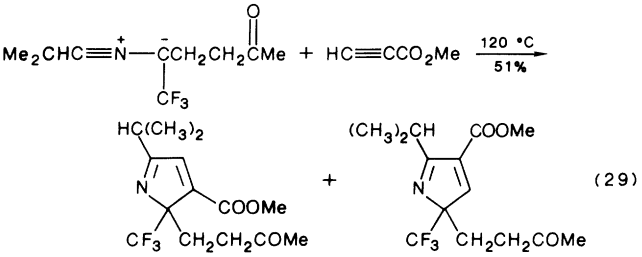
R, R[1] = H, Me, Et, Ph, etc.

An alternate route involves the reaction of a diene with a heterodienophile as with the electron-deficient imine in eq 28.[41]



(28)

3. 1,3-Dipolar Cycloadditions.[42] An important method of synthesizing a wide range of five-membered heterocyclic compounds is via 1,3-dipolar cycloadditions. Depending on the choice of 1,3-dipole and dipolarophile, highly substituted five-membered heterocycles with one or more heteroatoms can be prepared. Examples of 1,3-dipoles which participate in cycloadditions are nitrile ylides, nitrile oxides, azides, and nitrones.[4] Typical dipolarophiles are the same as dienophiles for Diels–Alder reactions, i.e., electron-deficient alkenes and alkynes. Compounds with multiple bonds containing heteroatoms can also function as dipolarophiles, e.g., imines, nitriles, and thiones. Representative examples of five-membered heterocycle synthesis by 1,3-dipolar cycloadditions are given in eq 29[43] and 30.[44]



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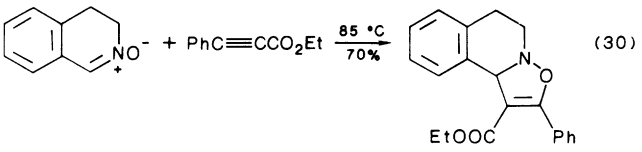


(30)

III. Implementation of Heterocycle Synthesis in CAMEO

An important aim of the CAMEO project is the formulation of generalized rules governing reactivity. This is accomplished primarily by extensive analysis of reactivity and selectivity trends found in quantitative and qualitative literature results. Subsequently, the rules are integrated into the program where their utility can be gauged. In the present case, processing is facilitated by recognizing that the reactions can be grouped by mechanistic class, i.e., addition, addition–elimination, and substitution, and then evaluated in a general manner rather than considering each reaction individually.

This section is a detailed account of the implementation of heterocycle-forming reactions in CAMEO. The scope of this module is discussed followed by a description of the current algorithms for treating heterocycle-forming reactions. The discussion centers on the determination of mechanistic class, nucleophile and electrophile perception and classification, and selectivity. The construction of intermediates and products using a method that features "heterocyclic extended mechanistic steps" has also been implemented, as presented here. The discussion concludes with representative reaction sequences produced by the program (section IV).

A. Scope of the Heterocyclic Module. The module is designed to encompass all the major types of heterocycle-forming reactions outlined in the previous section. The predominant class, i.e., additions, addition–eliminations, and substitutions under neutral and acidic conditions, is

(34) Hassner, A.; Fowler, F. W. *Tetrahedron Lett.* **1967**, 1545.
(35) Survey: Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*; Academic Press: New York, 1967. Patai, S., Ed. *The Chemistry of Ketenes, Allenes, and Related Compounds*; Wiley-Interscience: Chichester, 1980.
(36) Graf, R. *Ann.* **1963**, *661*, 111.
(37) Raasch, M. S. *J. Org. Chem.* **1970**, *35*, 3470.
(38) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
(39) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.
(40) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.
(41) Reference 38, p 3090.
(42) Review: Padwa, A., Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984.
(43) Steglich, W.; Gruber, P.; Heininger, H.-U.; Kneidl, F. *Chem. Ber.* **1971**, *104*, 3816.
(44) Huisgen, R.; Seidl, H.; Bruning, I. *Chem. Ber.* **1969**, *102*, 1102.

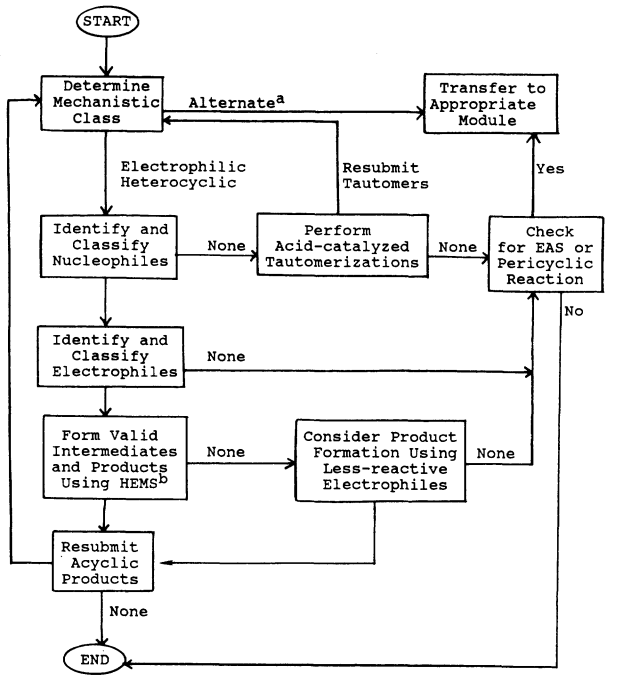


Figure 2. Outline of the processing of heterocyclic reactions in CAMEO. (a) Alternate refers to base-catalyzed/nucleophilic, electrophilic aromatic substitution, radical, carbenoid, or pericyclic. (b) HEMS = heterocyclic extended mechanistic step.

handled directly as discussed below. This reaction class is designated as "electrophilic heterocyclic" (EH). Classic examples are the Paal, Knorr, and Hinsberg syntheses. Additional examples can be found in section II.A.

The heterocyclic module also oversees the processing of reactions which are best treated by another mechanistic package in CAMEO. Thus, heterocycle syntheses that involve pericyclic,[4] base-catalyzed or nucleophilic reactions,[1] radical or carbenoid intermediates,[45,46] or electrophilic aromatic substitution[3] are automatically transferred to the appropriate module for processing. The mechanistic selection algorithm that performs this task is discussed below in section C. The heterocyclic module also handles multistep syntheses of heterocycles that involve more than one mechanistic class. Examples are the Fischer indole synthesis, Combes quinoline synthesis, and Guareschi–Thorpe pyridine synthesis. The treatment of such processes is discussed in the following.

B. Overview of the Processing of Heterocycle-Forming Reactions. The analysis of heterocycle-forming reactions in CAMEO involves several steps; therefore, prior to discussing the specifics of implementation, an overview is provided. The key considerations are determination of mechanistic class, perception of nucleophilic and electrophilic sites, intermediate and product formation, and resubmission of intermediates. An outline of the evaluation of heterocyclic reactions in CAMEO is given in Figure 2.

Given the input reactants and conditions, the first step is to determine the most probable mechanistic class for the reaction. The class selected for a reaction is either electrophilic heterocyclic or one of the alternate types discussed above. If the reaction is not in the electrophilic heterocyclic category, transfer is made to the appropriate package for processing.

The first important aspect in the evaluation of electrophilic heterocyclic reactions is perception and classification of nucleophiles. If no viable nucleophiles are perceived,

(45) Helson, H. E.; Hughey, M. R.; Jorgensen, W. L., to be published.
(46) Laird, E. R.; Rozas, R.; Jorgensen, W. L., to be published.

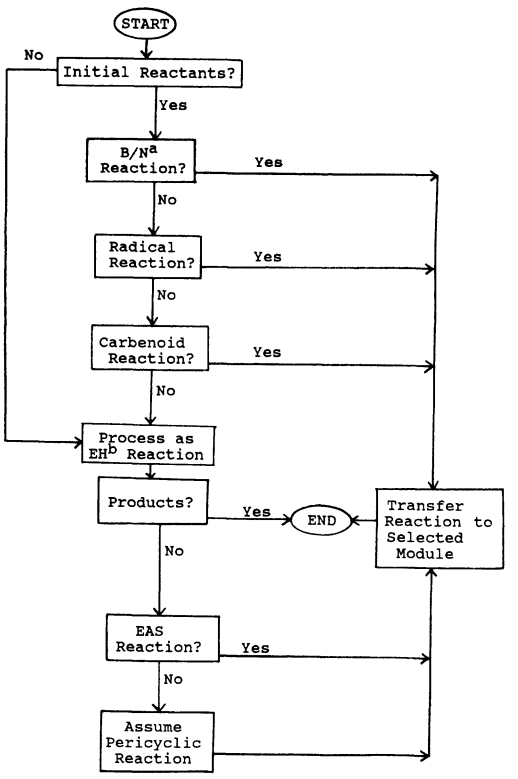
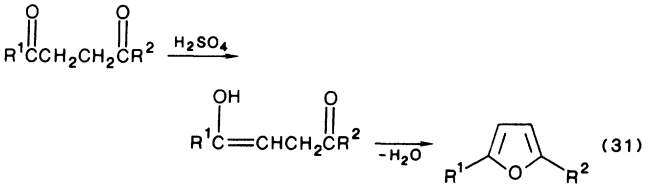


Figure 3. Outline of the determination of mechanistic class for heterocycle synthesis is CAMEO. (a) B/N = base-catalyzed/nucleophilic. (b) EH = electrophilic heterocyclic.

acid-catalyzed tautomerizations are performed because they may generate a reactive species. A common example of this occurs in the Paal furan synthesis (e.g., eq 31[11]),



(31)

which involves the enolization of a diketone. As shown in Figure 2, the tautomers are automatically resubmitted for further processing.

If reactive nucleophiles are identified by the program, then electrophile perception and classification are carried out. The absence of nucleophiles, electrophiles, or generated tautomers indicates that the starting materials should be considered by either the electrophilic aromatic substitution or the pericyclic packages.

Assuming reactive nucleophilic and electrophilic sites are found, the next step is product formation. At this point if attack at the most reactive electrophilic sites is deemed infeasible, then less-electrophilic sites are allowed to participate in the reaction (vide infra). Lastly, reactions which generate acyclic intermediates are resubmitted for further processing in order to complete the ring formation, if possible. The key aspects of this overview are discussed in detail below.

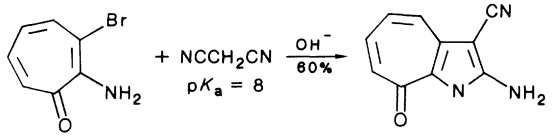
C. Determination of Mechanistic Class. In view of the variety of reaction types for heterocycle synthesis, an algorithm was developed to determine the most probable mechanistic class for the input reactants in order to direct the processing in CAMEO. The order in which the possible mechanistic types are considered is summarized in Figure 3. The specific order was chosen solely to facilitate implementation. All of the mechanistic classes are considered for the initially entered reactants. However, the options

Table III. Summary of the Rules Used To Determine Mechanistic Class for Potential Heterocycle-Forming Reactions

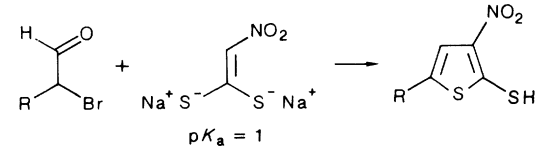
mechanistic class	rule
1. base-catalyzed nucleophilic	anion ($pK_a(H_2O) > 0$) present or can be generated
2. radical	radical center present or can be generated
3. carbenoid	carbene, nitrene present or can be generated
4. electrophilic heterocyclic	criteria in 1–3 not met
5. electrophilic aromatic substitution	no reaction from 4 and reactive aromatic system present
6. pericyclic	no reaction from 4 and no reactive aromatic system present, or no reaction from 5

are reduced for resubmitted reactions, i.e., for reactions of intermediates generated by the heterocyclic package (vide infra). In this case, the class is selected from electrophilic heterocyclic, electrophilic aromatic substitution, and pericyclic. Base-catalyzed/nucleophilic, radical, and carbenoid are not considered because the heterocyclic module does not generate anionic, radical, carbene, or nitrene intermediates. The rules used in the program to determine the mechanistic class are discussed below and summarized in Table III.

1. Base-Catalyzed/Nucleophilic. Heterocycle-forming reactions which involve either input or generated anions are best treated by the base–catalyzed/nucleophilic module. The criteria used to determine when this is appropriate are (1) if an anion whose conjugate acid has a predicted aqueous pK_a above 0 is present or generated or (2) if an anion can be formed via proton transfer from an acidic site to a neutral base, e.g., trialkylamines or pyridine.[1] Examples of heterocycle syntheses which fit into this category are presented in section II.A. and in eq 32–34.



(32)[47]



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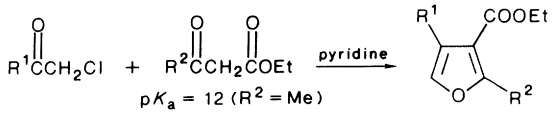


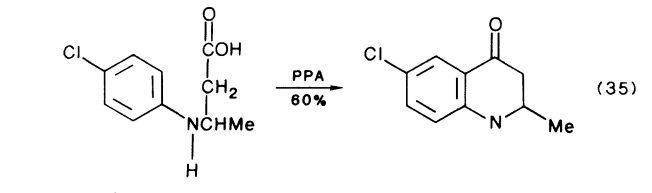
(34)[49]

2. Radical. If the check for a base-catalyzed/nucleophilic process is passed, the initial reactants are scanned for the presence of either an input radical center or a radical initiator, e.g. R_3SnH and AIBN. Reactions which fit into this category are transferred to the radical module for processing.[46]

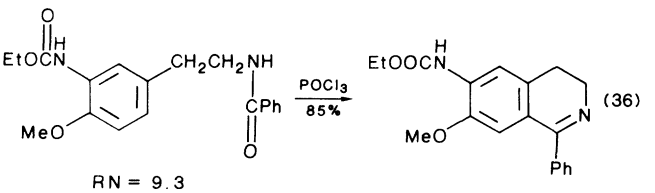
3. Carbenoid. If base-catalyzed/nucleophilic or radical is not selected as the mechanistic type, the initial reactants are searched for either the presence or potential generation of a carbene or nitrene center. Specifically, reactions commonly used to form carbenes and nitrenes, e.g. photochemical decomposition, are considered. When these conditions are encountered, the system is transferred to the carbenoid module for analysis.[45]

4. Electrophilic Heterocyclic. Reactants which do not meet the criteria for the above classes of reactions are then processed by the electrophilic heterocyclic module. This category covers the majority of heterocycle-forming reactions and its processing is discussed in sections D–F below. When a reaction is analyzed by this package and no products are predicted, the remaining classes, i.e., electrophilic aromatic substitution and pericyclic, are considered.

5. Electrophilic Aromatic Substitution. The criterion that keys this mechanistic type is that an activated aromatic ring must be present, i.e., the predicted reactivity number (RN) for the aromatic system must be greater than an equal to 1. Specifically, RN is the predicted log of the reaction rate for the aromatic ring relative to benzene (RN = 0) under the same conditions.[3] Naturally, an appropriate electrophile must be available to lead to product formation. Examples of heterocycle syntheses which fit into this category are given in eq 35[50] and 36[51] along with the predicted RN's.



(35)



(36)

6. Pericyclic. Finally, the reactants may be analyzed for possible pericyclic reactions when the following conditions are met: (1) the mechanistic type is not predicted to be base-catalyzed/nucleophilic, radical, or carbenoid; (2) a viable electrophilic heterocyclic reaction was not identified; and (3) an activated aromatic system is not present or no products were predicted by the electrophilic aromatic substitution package. Thus, pericyclic is the mechanistic class tried when all other current possibilities have been eliminated.

The remainder of this section focuses on the processing of electrophilic heterocyclic reactions in CAMEO. The key aspects of this discussion are the perception of nucleophilic and electrophilic sites, product formation, and selectivity.

D. Perception of Nucleophilic Sites. The classification of the nucleophilic and electrophilic sites is critical to the handling of selectivity by the program. For nucleophiles, the predominant alternatives for heterocycle synthesis contain reactive nitrogen, oxygen, or sulfur atoms. Most commonly utilized are binucleophiles such as hydrazines, ureas, semicarbazides, and hydrazides. Table I lists some additional binucleophiles, while examples of typical mononucleophilic reactants include amines, thiols, and alcohols.

Nucleophilic sites for EH reactions are recognized in a stepwise manner in CAMEO. Once they have all been perceived, they are rated and cataloged according to their reactivity. This information is then used to form the set of most reactive nucleophilic sites. The algorithm de-

(47) Taylor, E. C.; McKillop, A. *Adv. Org. Chem.* **1980**, *7*, 130.
(48) Henkiksen, L.; Autrup, H. *Acta. Chem. Scand.* **1970**, *24*, 2629.
(49) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167.
(50) Koo, J. *J. Org. Chem.* **1963**, *28*, 1134.
(51) Ishiwata, S.; Itakura, K. *Chem. Pharm. Bull.* **1969**, *17*, 2256.

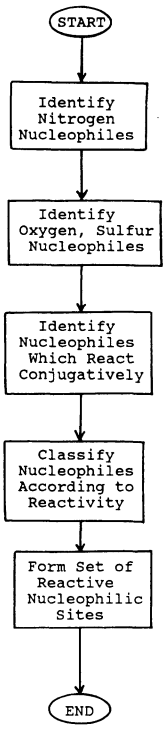
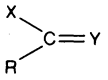


Figure 4. Overview of the perception of nucleophiles for electrophilic heterocyclic reactions.

veloped for the identification and classification of the nucleophilic sites is discussed below and summarized in Figure 4.

1. Identification of Nucleophiles. Reactive nitrogen nucleophiles such as amines, hydrazines, and hydroxyl amines are recognized first. Next identified are nitrogen-containing compounds in which the nucleophilic center is deactivated by an adjacent electron-withdrawing group, e.g., amides, ureas, guanidines, and thiosemicarbazides. Species containing nucleophilic oxygen or sulfur are subsequently identified. Examples are alcohols, enols, oximes, and thiols. Nucleophiles which can react conjugatively, e.g., enamines, enethiols, amidines, and thioamides, are recognized last. Nucleophilic species of this type have two potentially reactive centers, represented by atoms X and Y in eq 37. Additional examples of conjugate nucleophiles



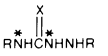
(37)

X = NH_2, NHR (OH, SH if Y = CHR)
Y = CHR, NH, NR, O, S
R = alkyl, aryl, or heterogroup

are given in Table I under the heading "1,3-systems." It is important to note that amides generally do not react as conjugate nucleophiles. Therefore, the oxygen atom of an amide is usually not considered as a conjugate nucleophilic site; however, exceptions are known and dealt with (vide infra). It should also be noted that for eventual product formation it is necessary that the nucleophilic site has an attached hydrogen, if it is not in a double bond, or that atom X has an attached hydrogen if the nucleophilic site is Y in eq 37. Thus, for example, ethers, tertiary amides, and sulfides are not considered.

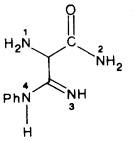
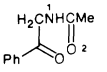
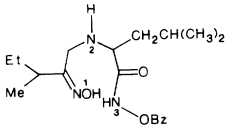
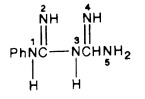
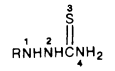
2. Classification and Ranking of Nucleophiles. The final step in the analysis is to construct the set of most reactive nucleophilic sites. For this purpose two categories are used. The first type, designated NUCTYP1, is comprised of reactive nucleophilic centers, i.e., the nucleophilic atom is not deactivated by an adjacent conjugating group.

Table IV. Examples of Compounds from the Two Categories of Nucleophiles[a,b]

NUCTYP1	NUCTYP2
H_2NR	
$HNRNH_2$	
H_2NOH	
$HNR(CH_2)_2NH_2$	RCH=CROH
RCH=CHNHR	RCH=CHNHR
ROH	
ArOH	
RSH	
ArSH	
	

[a] The atomic sites in the two categories are designated with an asterisk in potentially ambiguous cases. [b] X = NR, O, S.

Table V. Examples of Determining the Set of Most Reactive Nucleophiles, NUCATM, by Applying the Nucleophilic Site Reactivity Order

compound	NUCTY-P1	NUCTY-P2	NUCA-TM	ref
	1, 3	2, 4	1, 3	53
	1,[a] 2[a]		1, 2	54
	1, 2	3	2[b]	55
	2, 4	1, 3, 5	2, 4	56
	1, 3	2, 4	1, 3	57, 58

[a] The nitrogen and oxygen atoms of amides are considered to be NUCTYP1 when no reactive nitrogen sites are identified. [b] Atom 1 is eliminated as a NUCATM because N > O, S; see the nucleophilic site reactivity order.

Examples from this class are amines, thiols, alcohols, and the Y atoms in eq 37 for conjugate nucleophiles. Additional examples are given in Table IV.

Nucleophilic sites that are deactivated by an adjacent conjugating group comprise the second class. This type, termed NUCTYP2, is present in amides, ureas, and amidines, among other as listed in Table IV. Thus, nucleophilic sites from this category are generalized as atom X in eq 37. However, in the absence of unconjugated, nucleophilic nitrogen atoms, nitrogen atoms from the deactivated class are placed in NUCTYP1 (see the second entry in Table V for an example).

The nucleophilic sites can then be ranked according to reactivity as follows. Reactive N, O, and S sites (NUCTYP1) are more nucleophilic than deactivated (NUCTYP2) sites. Within the two nucleophile categories further distinctions can be made. The following nucleo-

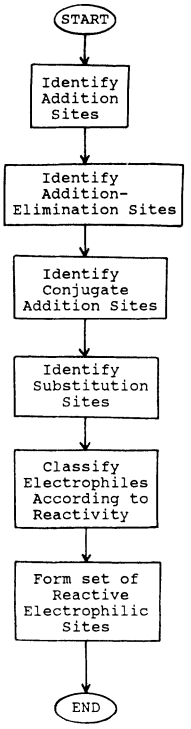


Figure 5. Outline of the perception of electrophiles for electrophilic heterocyclic reactions.

philicity order is imposed for NUCTYP1 sites: N > O, S, e.g., amines and hydrazines are more reactive than alcohols and thiols. The steric environment is also considered. Within each classification, nucleophilic atoms bearing bulky substituents are considered to be less reactive than sterically unhindered nucleophilic centers. For examples, for methylhydrazine both nitrogens are in the set of reactive nucleophilic sites, while for *tert*-butylhydrazine only the unsubstituted nitrogen is considered to be nucleophilic. However, a hindered nitrogen is still more reactive than an oxygen. The ranking for nucleophilic sites can then be summarized by the reactivity order given below.

NUCTYP1 (N > O, S), (unhindered > hindered) > NUCTYP2 (unhindered > hindered)

This order embodies selectivity trends observed in a wide range of heterocycle syntheses.[52] The set of reactive nucleophilic sites, NUCATM, is then formed by applying the reactivity order to all of the potentially reactive centers. Subsequently, only the most reactive group of nucleophilic sites is considered for processing. That is, the presence of NUCTYP1 nucleophiles causes NUCTYP2 nucleophiles to be ignored. Examples of determining the reactive sites for several compounds are given in Table V.

E. Perception of Electrophilic Sites. The predominant electrophilic species utilized in heterocycle synthesis feature addition and substitution sites. Examples include ketones, esters, acid and alkyl halides, and imines, among others as presented in the previous sections. Bielectrophilic reactants, e.g. dicarbonyl and α,β-unsaturated carbonyl compounds, are widely used (see Table I for additional examples). For molecules containing several electrophilic sites it is necessary to gauge their relative reactivity in order to determine which sites are most susceptible to nucleophilic attack. The identification and ranking of electrophiles for heterocyclic reactions are discussed below and outlined in Figure 5.

Table VI. Examples of Compounds in the Five Electrophile Categories

ATYP1	ATYP2	ATYP3
	RHC=O	RCOOH
	R_2C=O	RCOOR
R_2C=C=X (X = NR, O, S)		R_2C=NR
	RHC=S	RC≡N
Y=C=X (X, Y = NR, O, S)	R_2C=S	RSO_3R
		
		
ATYP4	SUBSIT	
	RCH_2LG	(LG = Cl, Br, I, NR_3^+, SR_2^+, OTs, OTMS, etc.)
(X = NR, O, S)	RHC=CH—LG	
RC≡CR	RNH—LG	
RC≡CC≡CR	RHC=N—LG	
	RS—LG	

1. **Identification and Classification of Electrophiles.** Electrophiles are identified and grouped according to reactivity in a stepwise manner in CAMEO. For the purposes of ranking, each class is assigned a label, i.e., ATYP1 to ATYP4 for addition sites and SUBSIT for substitution sites. Highly electrophilic species (ATYP1) such as acid halides, heterocumulenes, and anhydrides are identified first. At this time, due to the lack of precedents, unactivated allenes are not considered electrophilic. Electrophiles in which the reactive site is a C=X (X = O, S) bond without an adjacent group that can be eliminated, e.g., aldehydes, ketones, and thiones are recognized next (ATYP2). This is followed by the identification of species containing a O=XOR (X = C, S) group such as carboxylic acids and esters, and sulfinate and sulfonate esters. The electrophilic sites in multiple C–N bonds, e.g. imines and nitriles, are also perceived at this time. This class is labeled ATYP3. The least reactive addition sites (ATYP4), e.g. amides and alkynes (including diynes), are recognized next. Lastly, each group of addition sites is augmented by including conjugate positions, e.g. in α,β–unsaturated carbonyl compounds.

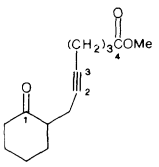
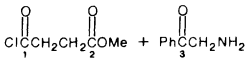
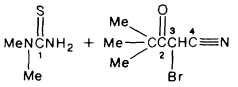
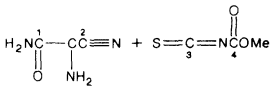
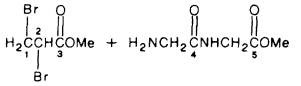
The reactants are then scanned for the presence of substitution sites (SUBSIT). These are defined as a singly or doubly bonded, 1° or 2° C, N, or S atom bearing a good leaving group. A tertiary carbon atom with a good leaving group is considered as a potential substitution site only for intramolecular reactions. Examples of groups with sufficient leaving ability are Cl, Br, I, NR_3^+, SR_2^+, PR_3^+, OSO_2R, and $OSiR_3$. Sample compounds in the five categories of electrophiles are shown in Table VI.

2. **Ranking of Electrophilic Sites.** The final aspect of electrophile perception is to form the set of most reactive sites. After the potential electrophilic sites are placed into the categories described above, the following reactivity order is then invoked:[59]

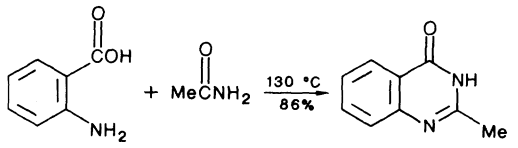
ATYP1 > SUBSIT, ATYP2 > ATYP3 > ATYP4

(52) A database of over 1000 representative heterocycle syntheses was used in determining the reactivity order. Many examples from this database can be found throughout the paper.
(53) Barlin, G. B. *The Pyrazines*; Wiley: New York, 1982; p 34.
(54) Lakhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 102.
(55) Joule, J. A., Smith, G. F. *Heterocyclic Chemistry*; VanNostrand Reinhold: London, 1978; p 142.
(56) Modest, E. J. In *Heterocyclic Compounds*, Vol. 7; Elderfield, R. C., Ed.; Wiley: New York, 1961; p 663.
(57) Airsworth, C. *Org. Synth.* **1960**, *40*, 99.
(58) Bhagwat, V. S.; Nargund, K. S. *J. Indian Chem. Soc.* **1968**, *45*, 270.

Table VII. Examples of Determining the Set of Most Reactive Electrophilic Sites (REACST) by Applying the Electrophilic Site Reactivity Order

reactants	classification of electrophilic atoms	REACST	ref
	ATYP2: 1 ATYP3: 4 ATYP4: 2, 3	1	61
	ATYP1: 1 ATYP2: 3 ATYP3: 2	1	62
	SUBSIT: 3 ATYP2: 2 ATYP3: 4 ATYP4: 1	2, 3	63
	ATYP1: 3 ATYP3: 2, 4 ATYP4: 1	3	64
	SUBSIT: 1, 2 ATYP3: 3, 5 ATYP4: 4	1, 2	65

In general, only the sites in the most reactive class present are considered for processing. That is, electrophiles located higher in the reactivity order cause those lower in the order to be ignored. However, there is an important exception to this rule. Specifically, is no viable products can be formed by using the most reactive electrophiles, reactions with the next most reactive sites are considered. A representative example occurs in Niementowski's 4-oxoquinazoline synthesis shown in eq 38.[60] Here, the car-



(38)

boxylate and amide carbons are identified as potential electrophilic sites in ATYP3 and ATYP4, respectively. However, intramolecular addition–elimination at the carboxylic acid site is disfavored relative to the intermolecular pathway. Therefore, attack at the less-reactive electrophilic site is considered. Intermolecular addition of the amine (the most reactive nucleophilic site) to the amide followed by cyclization provides the 4-oxoquinazoline. The four-membered ring formation is rejected and only the intermolecular pathway is predicted by the program as observed.[60] Additional examples of determining the most reactive electrophilic sites for several compounds used in heterocycle syntheses are presented in Table VII. The reactive nucleophilic and electrophilic sites are then channeled to a routine which forms intermediates and products of heterocyclic reactions, as discussed below.

F. Product Formation. The final aspect of analyzing electrophilic heterocycle-forming reactions in CAMEO is the generation and processing of intermediates and products. All combinations of the most reactive nucleophilic and electrophilic sites are considered to yield the potential products. The viability of each nucleophilic/electrophilic site pairing is then assessed and only the most probable products are formed and displayed. The key aspects of product formation are the following: (1) determination of ring-size selectivity and identification of disfavored pathways; (2) application of the appropriate mechanistic steps needed to construct the product, i.e., by utilizing heterocyclic extended mechanistic steps; and (3) resubmission of acyclic intermediates and products for further processing. Each of these important issues is discussed in detail below. A simple outline of the program flow for the formation of products is given in Figure 6.

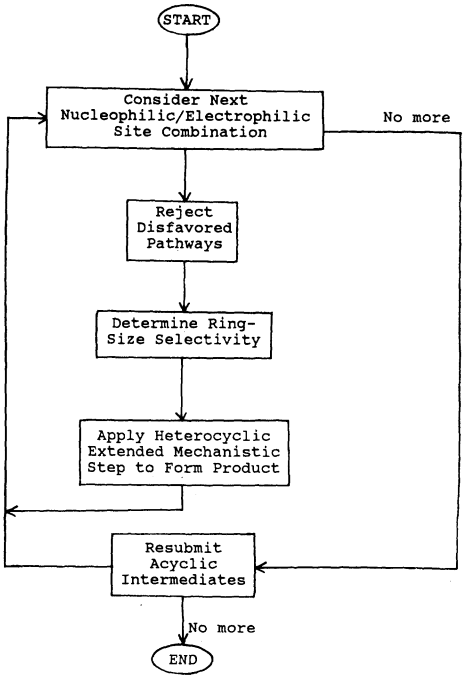


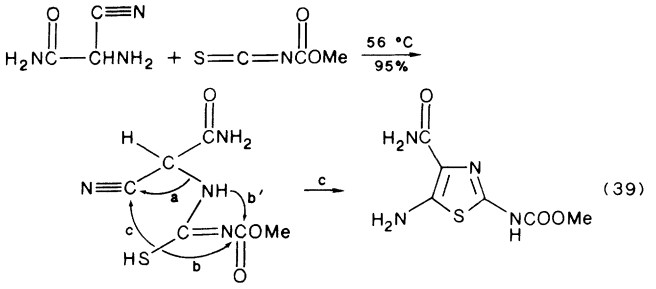
Figure 6. Outline of the formation of products for electrophilic heterocyclic reactions.

1. Ring-Size Selectivity. The common scheme in many heterocycle syntheses is intermolecular addition of a binucleophilic species to a bielectrophilic reactant to form an acyclic intermediate, which then cyclizes. However, several intramolecular reaction pathways, leading to dif-

(59) Analogous to nucleophile ranking (ref 52), the reactivity order is based on electrophile selectivity trends observed for a large number of representative heterocycle syntheses.

(60) Armarego, W. L. F. *J. Appl. Chem.* **1961**, *11*, 70.
(61) Richardson, K. A.; Saunders, J.; Taylor, R. J. K. *Tetrahedron Lett.* **1985**, *26*, 1171.
(62) Lakhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 104.
(63) Birkinshaw, T. N.; Gillon, D. W.; Shaun, H. A.; Meakins, G. D.; Tirel, M. D. *J. Chem. Soc., Perkin Trans. 1* **1984**, 147.

ferent ring sizes, are often available to the intermediate. For example, in the thiazole synthesis shown in eq 39,[64]



(39)

the construction of three-, four-, and five-membered heterocyclic rings can be envisioned via paths a–c, respectively. As discussed in section II, electrophilic heterocycle-forming processes generally exhibit the familiar trends for ring-size selectivity. Thus, formation of five- and six-membered rings is usually more favorable than three-, four-, and seven-membered ring closure. Accordingly, the ranking of cyclization pathways with respect to the size of the ring formed used in the program is given below. Note that

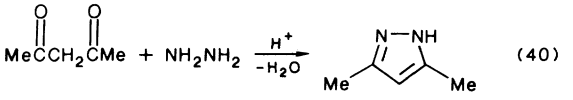
$$5, 6 > 3, 4, 7 > 8$$

entropic factors render the formation of heterocyclic rings of size larger than eight via intramolecular cyclization difficult. It should also be noted that the current module in CAMEO only handles the synthesis of three- through eight-membered heterocyclic rings via the electrophilic routes. Furthermore, the most favorable cyclization pathways are deemed dominant, e.g., successful formation of a five- or six-membered ring would cause pathways to other ring sizes to be ignored. This rule is based on the analysis of many precedents in the literature.[7-13]

Along with the size of the new ring, in some cases it is important to consider the type of electrophilic site involved in the cyclization. Formation of three- and four-membered heterocyclic rings via intramolecular reactions generally occurs only in activated systems. Specifically, such ring closures require attack on a reactive electrophilic site, e.g., in an acid halide, anhydride, or alkyl halide. Consequently, three- and four-membered cyclization pathways involving closure at less-reactive sites, i.e., ATYP2 to ATYP4 (vide supra), are rejected by the program. This condition reinforces the formation of the five-membered ring in eq 39, which is consistent with the observed yield of 95% for the thiazole.[64]

Each nucleophilic/electrophilic site combination is processed as described above. Combinations which are not rejected are passed to the next step in product formation, as discussed below. It is important to emphasize that selectivity is achieved by careful selection of the most reactive nucleophilic and electrophilic sites and of the most favorable cyclization pathways.

2. Heterocyclic Extended Mechanistic Steps. Prior to the implementation of the heterocyclic module, nucleophilic and electrophilic reactions in CAMEO have been generated as a combination of fundamental mechanistic steps, e.g. proton transfer, substitution, addition, and elimination. Starting materials were allowed to undergo one to three fundamental steps to create the first set of products. These products or intermediates could then be resubmitted by the user for further processing. Though this approach works well for base-catalyzed and nucleophilic processes,[1] it is problematic for electrophilic heterocyclic reactions. To illustrate, consider the simple pyrazole synthesis shown in eq 40.[11] As depicted in Figure

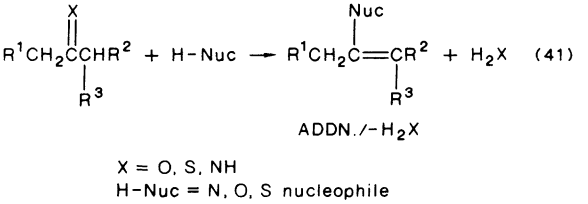


(40)

7, this representative reaction involves a relatively large number of fundamental steps. The major problem under acidic conditions is the frequent proton transfer and dehydration steps. The key intermediate in reaction 40 is structure 1; clearly, it is impractical to construct and display the other intermediates. Therefore, the need for a new approach to product formation for electrophilic heterocycle-forming reactions was evident. For efficiency, it is clearly desirable to take advantage of the small number of fundamental reaction types noted above in section II rather than have specific code for many named reactions that are mechanistically similar.

The method developed involves combining many of the individual steps of an electrophilic heterocyclic reaction into one extended mechanistic step. Such extended steps have been formulated for each of the major types of electrophilic heterocyclic reactions, i.e., addition, addition–elimination, and substitution, as described below and summarized in Table VIII.

a. Addition. The mechanistic steps involved in addition to a C=O group under electrophilic conditions are illustrated in Figure 7. In an analogous manner, acid-catalyzed addition to a C=NH or C=S bond can result in the loss of NH_3 or H_2S, respectively. Thus, the heterocyclic extended mechanistic step (HEMS) for addition to C = X (X = O, S, NH) is comprised of the following steps: protonation, addition, proton transfer, and loss of a small fragment, i.e., H_2O, H_2S, or NH_3. This HEMS is represented in eq 41 for a reaction involving a typical



(41)

heteronucleophile (vide supra). Two typical examples of this addition process combine to yield the pyrazole syn-

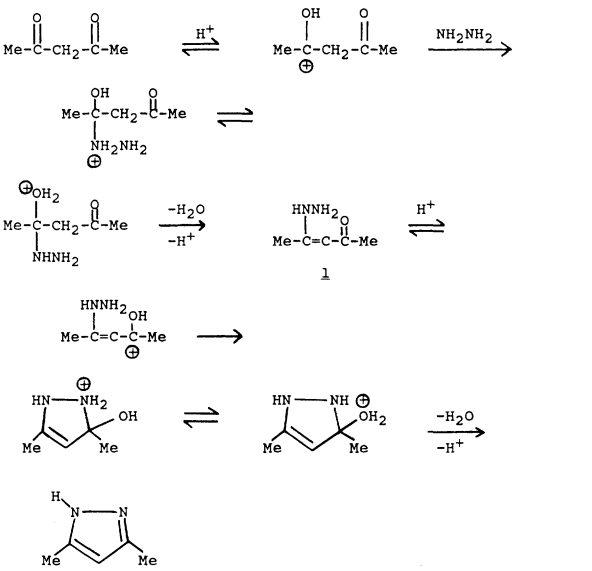
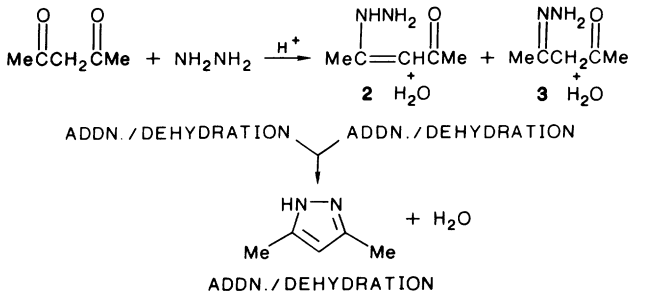


Figure 7. Mechanistic steps in a representative electrophilic heterocycle synthesis.

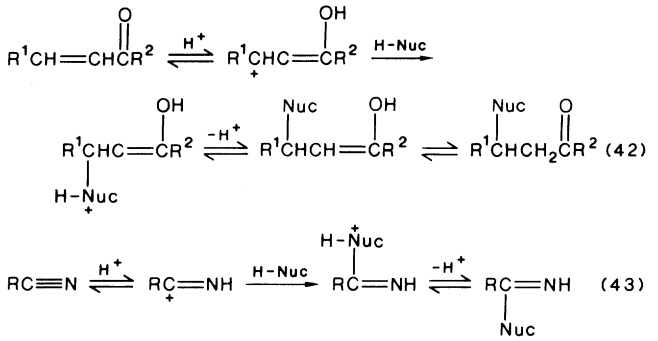
(64) Esmail, R.; Kurzer, F. *Synthesis* **1975**, 301.
(65) Eremeev, A. V.; Krutius, O. *Khim. Geterotsikl. Soedin.* **1982**, 1627.

Scheme I



thesis shown in eq 40 and Figure 7. Processing of this reaction by the heterocyclic module and application of the addition/dehydration HEMS results in output of the intermediates **2** and **3** and the product given in Scheme I. In practice, products are generated via the automatic resubmission of intermediates, as discussed in the following section. Note that for addition of a H_2NR nucleophile to a C=X compound, the program gives both the enamino and imino form of the product. The reactions in eq 41 and Scheme I reflect another feature of this addition HEMS. Specifically, in cases where loss of the small fragment can result in double-bond isomers, only the most substituted double bond is formed.

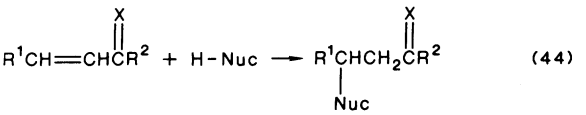
The other major class of addition reactions used in heterocycle synthesis involves attack at C=C, C≡C, and C≡N bonds, as in α,β-unsaturated carbonyl compounds and nitriles. Here, under acidic conditions, addition of a nucleophile is facilitated by protonation of the electrophile, e.g., eq 42 and 43. Thus, the mechanistic steps which



(42)

(43)

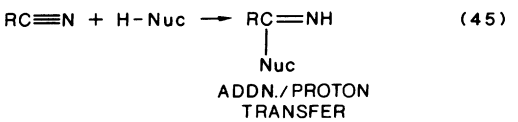
comprise the HEMS are protonation, addition, and proton transfer. This HEMS is represented in eq 44 and 45 for



(44)

ADDN./PROTON TRANSFER

X = O, S, NR

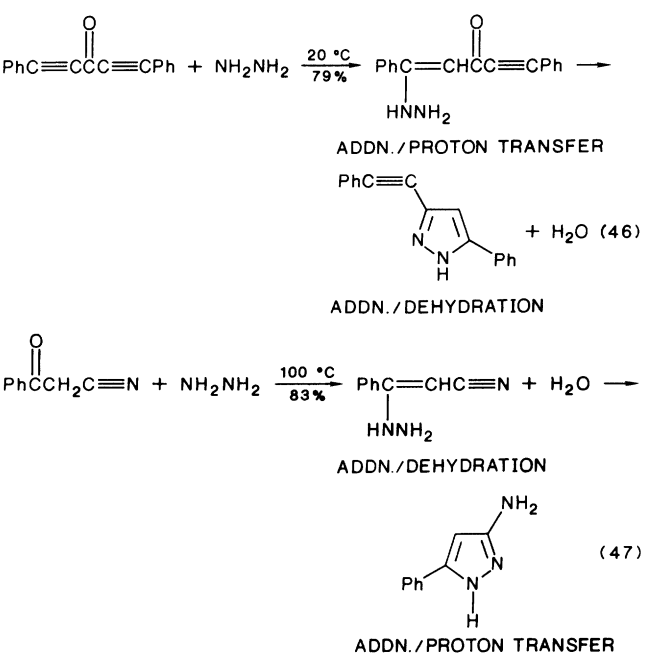


(45)

ADDN./PROTON TRANSFER

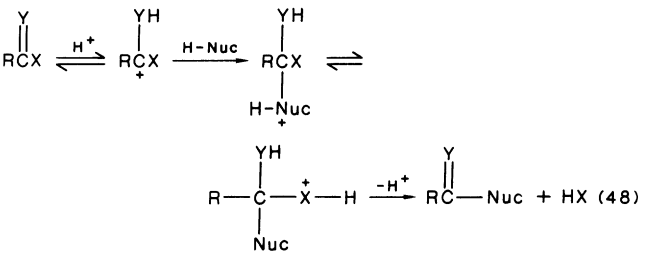
addition of a heteronucleophile, H-Nuc, to an α,β-unsaturated compound and a nitrile, respectively. Representative examples of these processes and the intermediates and products output by the program are presented in eq 46[66] and 47.[67]

b. Addition–Elimination. Addition of heteronucleophiles to acids, esters, and acid halides, etc., is followed by elimination of a leaving group, e.g., RO^-, Cl^-, Br^-, etc. The mechanistic steps in protic media for this process are illustrated in eq 48. Hence, the addition–elimination



(46)

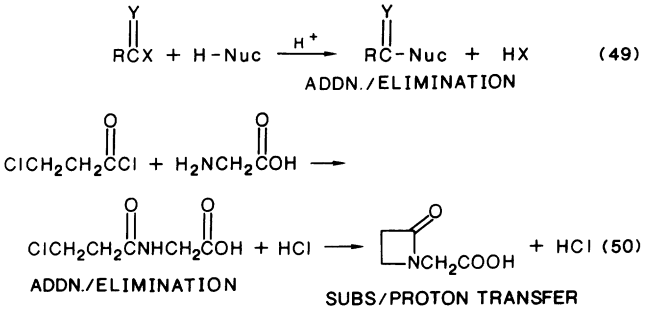
(47)



(48)

Y = O, S, NR; X = OR, halogen, etc.

HEMS consists of protonation, addition, proton transfer, and elimination, as represented in eq 49. A sample addition–elimination reaction as processed by the heterocyclic module is shown in eq 50.[68]



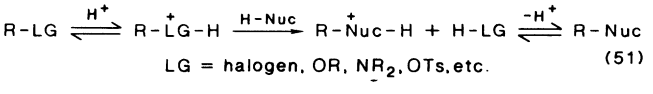
(49)

ADDN./ELIMINATION

(50)

ADDN./ELIMINATION SUBS/PROTON TRANSFER

c. Substitution. Under acidic conditions, the leaving ability of the displaced group in a substitution can be enhanced by protonation, e.g., eq 51. Thus, the HEMS



(51)

for substitution reactions is comprised of the following mechanistic steps: protonation, substitution, and proton transfer. This HEMS is represented in eq 52 for substitution by a typical heteronucleophile, H-Nuc. Repre-

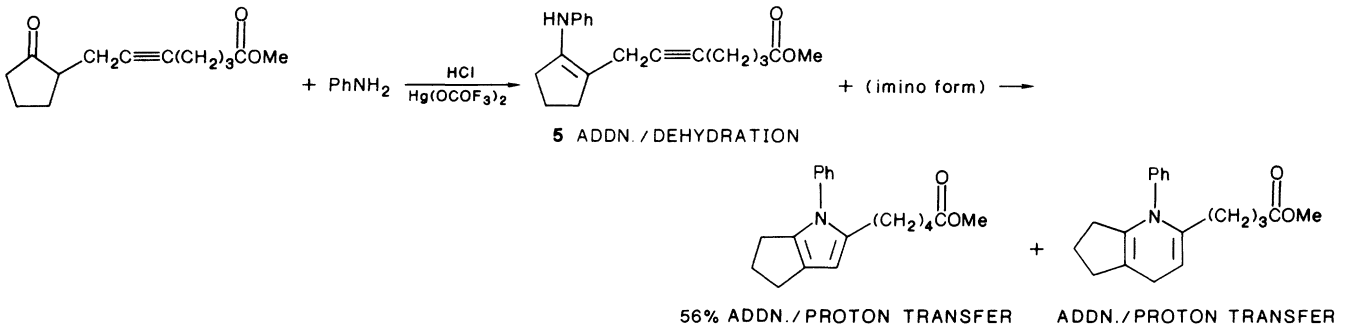
(66) Reimlinger, H.; Vandewalle, J. J. M. *Liebigs Ann. Chem.* **1968**, 117.

(67) El Nagadi, M. H.; Elmoghayer, M. R. H.; Elgemeie, G. E. H. *Synthesis* **1984**, 1.

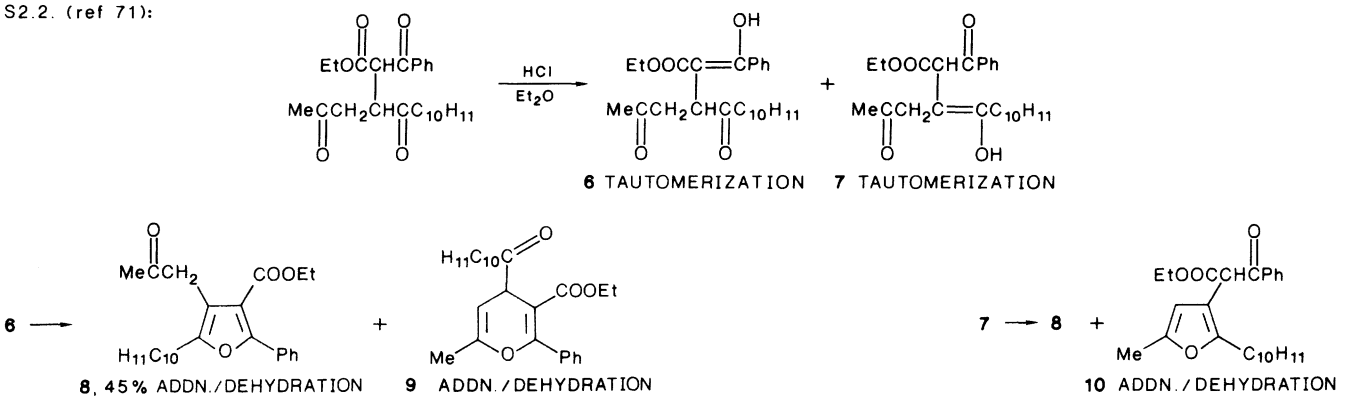
(68) Okawara, T.; Matsada, T.; Noguchi, Y.; Furukawa, F. *Chem. Pharm. Bull.* **1982**, *30*, 1574.

Scheme II

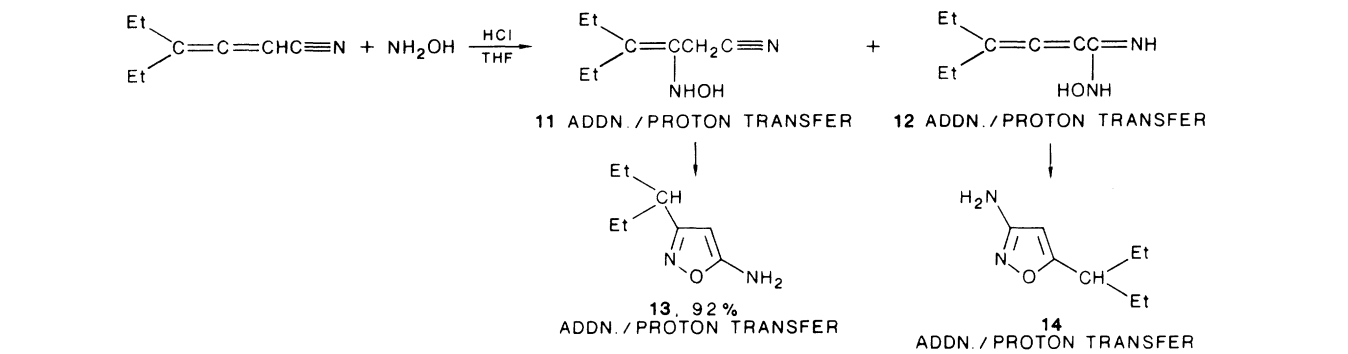
S2.1. (ref 61):



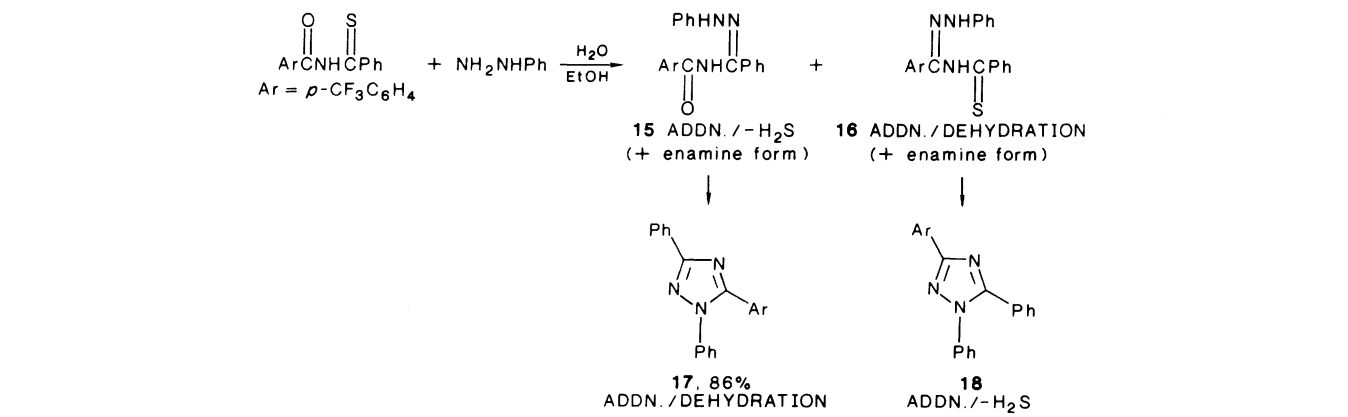
S2.2. (ref 71):



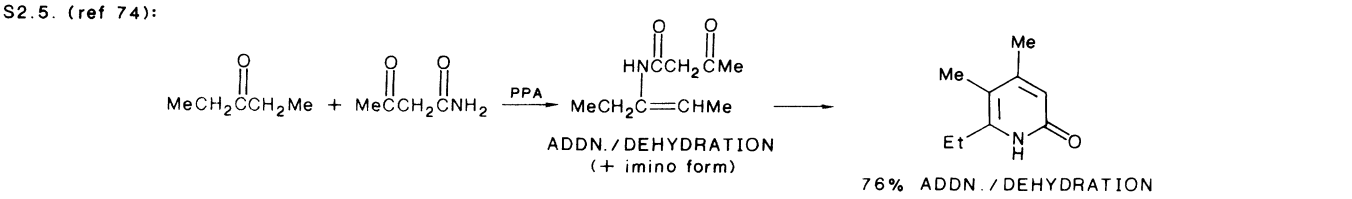
S2.3. (ref 72):



S2.4. (ref 73):

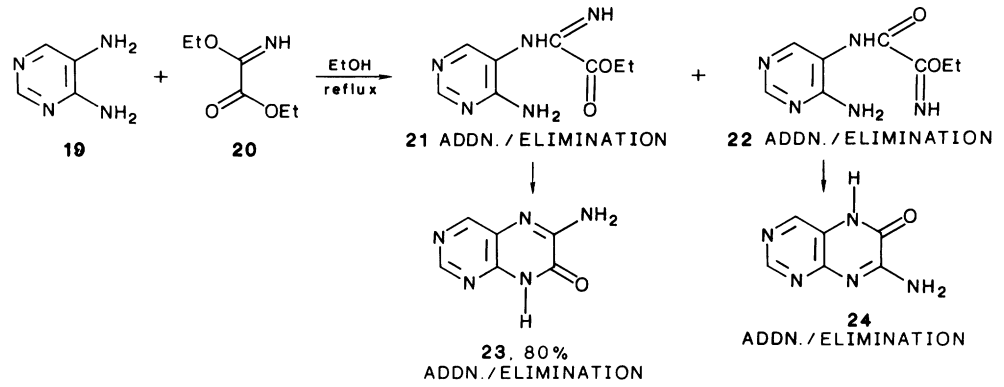


S2.5. (ref 74):

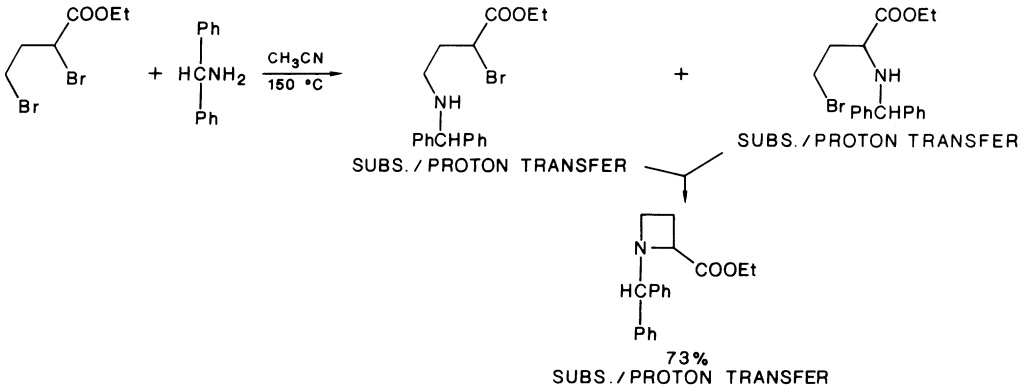


Scheme II (continued)

S2.6. (ref 75):

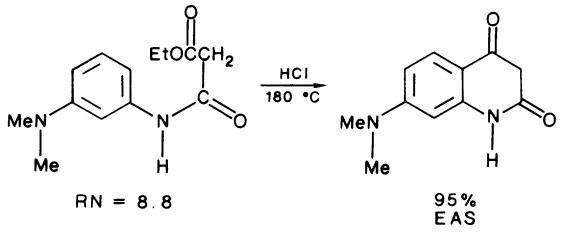


S2.7. (ref 76):

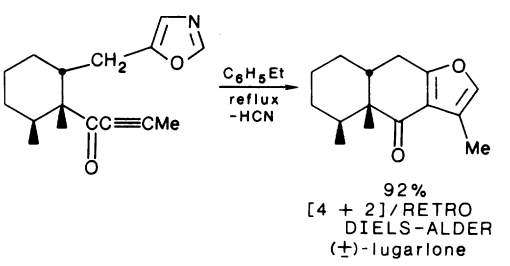


Scheme III

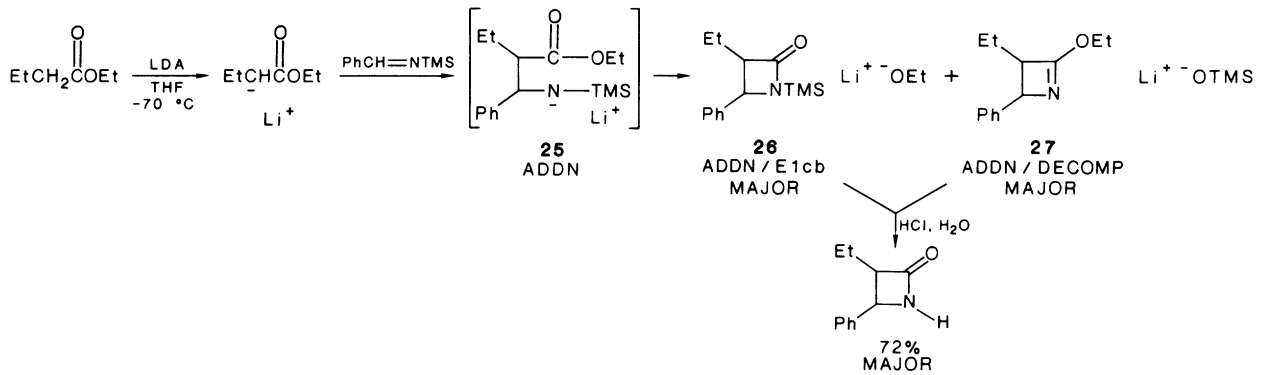
S3.1. (ref 79) ELECTROPHILIC AROMATIC:



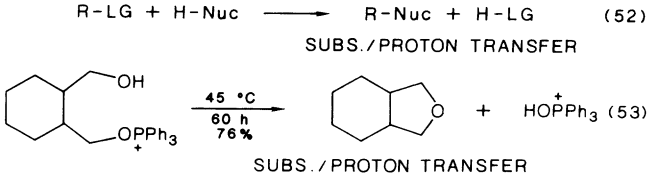
S3.2. (ref 80) PERICYCLIC:



S3.3. (ref 81) BASIC/NUCLEOPHILIC:



sentative syntheses involving substitution as processed by the heterocyclic module are shown in eq 50 and 53.[69]



3. Resubmission of Intermediates. When processing heterocycle-forming reactions in CAMEO, it is desirable to generate the predicted heterocyclic products in one pass through the program. This is accomplished by performing an automatic resubmission of any acyclic structures formed by the heterocyclic module. For example, consider the

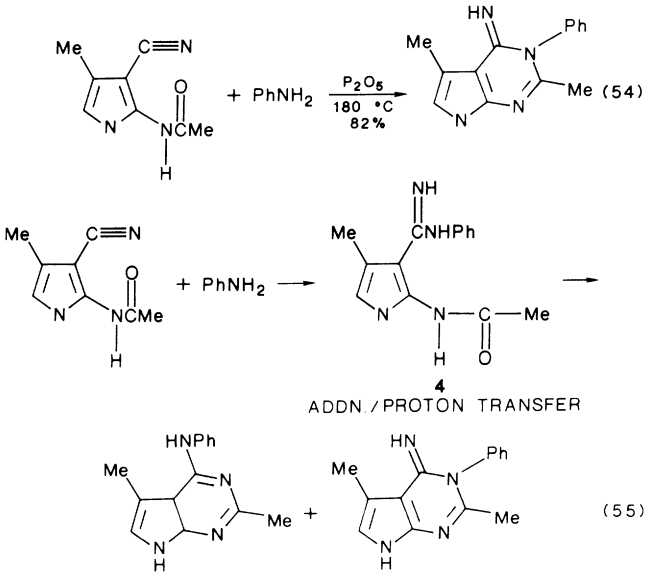
(69) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 5210.

Table VIII. Mechanistic Steps Comprising the HEMS for Each Type of Electrophilic Heterocyclic Reaction

type of reaction	mechanistic steps[a]	label[b]
addition/dehydration	protonation, addition, proton transfer, dehydration	ADDN./DEHYDRATION
addition/loss of NH_3	protonation, addition, proton transfer, $-NH_3$	ADDN./$-NH_3$
addition/loss of H_2S	protonation, addition, proton transfer, $-H_2S$	ADDN./$-H_2S$
addition/proton transfer	protonation, addition, proton transfer	ADDN./PROTON TRANSFER
addition/elimination	protonation, addition, proton transfer, elimination	ADDN./ELIMINATION
substitution	protonation, substitution, proton transfer	SUBS./PROTON TRANSFER

[a] Mechanistic steps under acidic conditions. In each case, under neutral conditions the protonation step is not operative. [b] Label output by the program during product display.

pyrimidine synthesis shown in eq 54.[70] The entire reaction sequence, as output by the program, is presented in eq 55.



Thus, processing of the starting materials gives an intermediate, **4**, which is automatically resubmitted for further analysis. Both **4** and the final products are displayed to the user and are stored in the synthetic tree. It is important to note that resubmitted intermediates are accorded the same treatment as initial reactants. In this case, structure **4** is predicted to undergo addition/dehydration reactions to provide the fused pyrimidines. Incidentally, both amidine nitrogens in **4** are placed in the NUCTYP1 class since no nitrogens are present that are not deactivated by conjugation.

IV. Sample Sequences

In order to illustrate more thoroughly the manner of analysis, several examples of predictions made by the program are considered in detail in this section. The examples were selected from the recent literature and are representative of typical heterocycle syntheses. All intermediates and products of electrophilic heterocyclic reactions predicted by CAMEO are shown in each case. Experimental yields are included when available. Three types of reaction sequences are presented: electrophilic heterocyclic (Scheme II), reactions processed by a module in CAMEO other than heterocyclic (Scheme III), and synthesis involving more than one mechanistic class (Scheme IV).

1. Scheme II. Electrophilic Heterocyclic Reactions. Taylor's keto–alkyne cyclization route to pyrrole analogues of prostacyclins is shown in example S2.1.[61] Here, the program predicts initial attack only at the ketone due to the greater electrophilicity of this site compared to the alkyne and ester. Note that addition at this site produces only the most substituted double bond. Automatic resubmission of the intermediate (**5**) gives both a pyrrole after tautomerization and the six-membered heterocycle, from endo addition. Only the pyrrole is reported, in 56% yield.[61] Reaction at the more electrophilic center, the ester, is rejected because this would lead to the formation of a ten-membered ring. This method has also been employed in the synthesis of the corresponding furan and thiophene.[61]

The second example, S2.2, is a Paal-type synthesis of a tetrasubstituted furan.[71] This reaction illustrates the program's ability to recognize and perform a necessary acid-catalyzed tautomerization. Although several tautomerizations are possible, only the most stable enols are formed. Both intermediates, **6** and **7**, are predicted to cyclize to a furan. Note that **6** reacts to form the only reported product (**8**, 45%).[71] Six-membered ring closure is considered as favorable as five-membered by the program, as evidenced by the pyran **9** also obtained from intermediate **6**. Note too that **7** reacts to form both the observed furan **8** and a trisubstituted isomer, **10**.

A selective reaction of the more nucleophilic center is illustrated in example S2.3.[72] Specifically, the program predicts initial attack by only the nitrogen of hydroxylamine to form intermediates **11** and **12**. Cyclization of **11** followed by aromatization leads to the only observed product (**13**, 92%).[72] An alternate route, generating an isomer of **13**, is also considered viable by the program. Thus, initial 1,2-addition to the nitrile instead of 1,4-addition gives **12**, which then cyclizes and subsequently tautomerizes to aminoisoxazole **14**.

A synthesis of a 1,2,4-triazole via an improved Einhorn–Brunner reaction is illustrated in example S2.4.[73] Here, the program predicts a mixture of products due to the asymmetry of the starting material. Addition of the hydrazine to the C=S and the C=O sites provides intermediates **15** and **16**, respectively. Subsequent cyclization of **15** gives the only reported product (**17**, 86%[73]), while **16** undergoes ring closure to an isomeric product, **18**. Additional pathways (not shown) to **17** and **18** are also proposed by the program. Specifically, attack by the other nucleophilic center, i.e., the N-phenyl nitrogen, also leads to the two 1,2,4-triazoles. This method has also been used to synthesize the corresponding 1,2,4-oxadiazoles.[73]

A useful synthesis of pyridones is provided by the condensation of acetoacetamide with a ketone, as in example S2.5.[74] Reaction of acetoacetamide with 3-pentanone in

(70) Girgis, N. S.; Jorgensen, A.; Pedersen, E. B. *Liebigs Ann. Chem.* **1983**, 2066.

(71) Antonioletti, R.; D'Auria, M.; Piancatelli, G.; Scettri, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2398.

(72) Fomum, Z. T.; Asobo, P. F.; Landor, S. R.; Landor, P. D. *J. Chem. Soc., Perkin Trans 1* **1984**, 1079.

(73) Lin, Y.; Hlavka, J. J.; Panayota, B.; Lang, S. A. *J. Heterocycl. Chem.* **1983**, *20*, 1693.

(74) Kato, T.; Sato, M.; Noda, M.; Itoh, T. *Chem. Pharm. Bull.* **1980**, *28*, 2244.

the presence of an acid catalyst gives the enamine. Subsequent cyclization at the acetyl group provides the only predicted and observed product. Note that both carbonyl carbons in the starting amide are potential electrophilic sites; however, the formation of a six-membered ring is much more facile than four-membered ring formation. Consequently, the latter process is rejected by the program. Thus, this illustrates the program's ability to favor an intermolecular reaction over a potential intramolecular reaction on the basis of ring size.

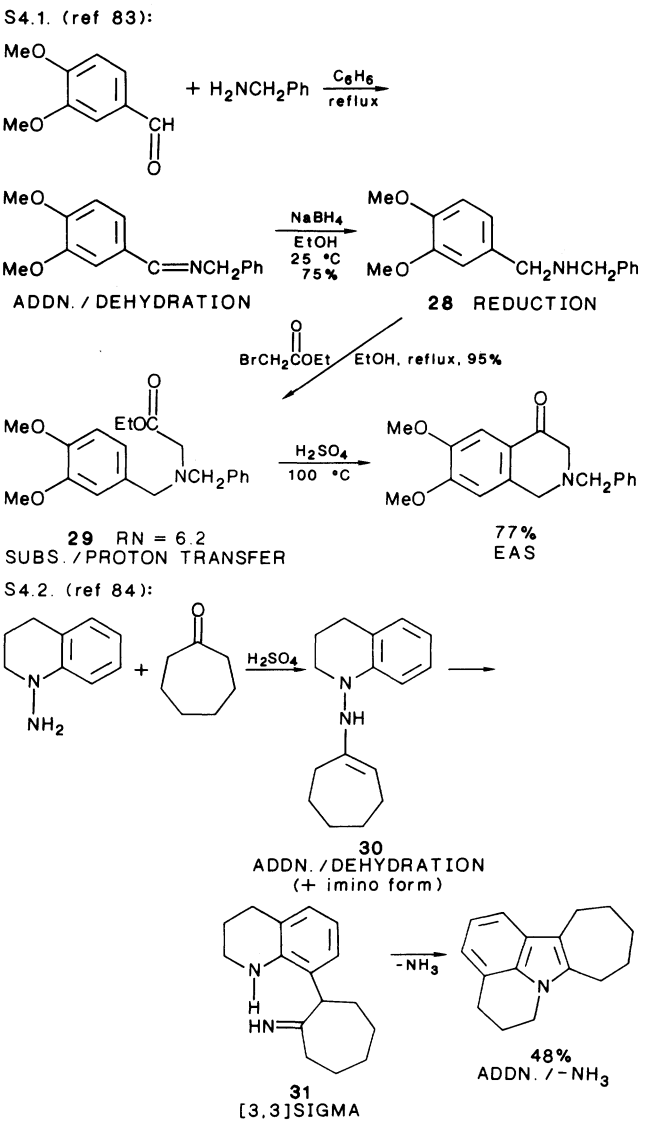
Ortho diamines, e.g. **19**, are widely used in the synthesis of fused pyrazines, as illustrated by example S2.6.[75] Here, as in example S2.4., the unsymmetrical reactants lead to a mixture of products. Specifically, attack by the diamine at both electrophilic sites of ethylcarbethoxyformimidate (**20**) is predicted by the program. Cyclization of intermediate **21** gives the only reported product (**23**, 80%[75]), while **22** closes to the isomer **24**. Note that an analogous series of reactions involving the other amino group (predicted by the program but not shown) also leads to compounds **23** and **24**. Imidate **20** has been utilized in the synthesis of a wide variety of heterocyclic systems.[75]

Intramolecular displacement by a nucleophilic heteroatom is a common route to three- and four-membered heterocyclic ring compounds. An example is the azetidine ester synthesis presented in S2.7.[76] Here, displacement of both the primary and secondary bromides by the amine is predicted by the program. Subsequent intramolecular substitution for both intermediates provides the only predicted and observed product.[76] Wasserman and coworkers have used this method to prepare several azetidine esters which can be readily transformed to the corresponding β-lactams.[76,77]

2. Scheme III. Heterocycle-Forming Reactions Processed by Other Modules in CAMEO.[78] The formation of a 2-quinolone via an intramolecular electrophilic aromatic substitution (EAS) is presented in example S3.1.[79] Here, potential nucleophilic and electrophilic sites, i.e., in the amide and the ester, are identified by the program; accordingly a mechanistic type of heterocyclic is initially assigned to the reaction. However, four-membered ring formation by an intramolecular addition/elimination on an ester is rejected by the heterocyclic module. At this point the program recognizes that a reactive aromatic system (RN = 8.8[3]) is present; therefore, the reaction is automatically transferred to the EAS package for processing. An intramolecular EAS reaction is predicted to yield only the less-crowded fused product, as observed.[79]

A reaction which ends up being processed by the pericyclic module is presented in example S3.2.[80] Here, no nucleophiles are identified, nor is a reactive aromatic system perceived. Therefore, transfer is made to the pericyclic module for evaluation. The program predicts that the acetylene and oxazole will undergo an intramolecular [4 + 2] cycloaddition followed by expulsion of HCN to give the only predicted and observed product.[80] Jacobi and co-workers have used this "bis heteroannulation" method in the synthesis of several related compounds.[80]

Scheme IV



A base-catalyzed β-lactam synthesis involving condensation of an imine with an ester is presented in example S3.3.[81] Recognition of the potential generation of a lithium ester enolate causes this reaction to be transferred to the base-catalyzed/nucleophilic module for processing. Addition of the enolate to the *N*-trimethylsilyl imine provides intermediate **25**. Two pathways are then predicted for reaction of this intermediate. Addition followed by loss of ethoxide forms the *N*-TMS β-lactam **26**, while addition and elimination of $(CH_3)_3SiO^-$ give the ethoxy 2,3-dihydroazete **27**.[82] Interestingly, upon workup in aqueous HCl, both **26** and **27** give the observed[81] N-unsubstituted β-lactam.

3. Scheme IV. Syntheses Involving More Than One Mechanistic Class. A useful feature of the heterocyclic module is its ability to process multistep syntheses

(75) McKillop, A.; Henderson, A.; Ray, P. S. *Tetrahedron Lett.* **1982**, *23*, 3357.

(76) Wasserman, H. H.; Lipshutz, B. H.; Tremper, A. W.; Wu, J. S. *J. Org. Chem.* **1981**, *46*, 2991.

(77) Wasserman, H. H.; Hlasta, D. J.; Tremper, A. W.; Wu, J. S. *J. Org. Chem.* **1981**, *46*, 2999.

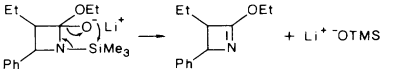
(78) The CAMEO modules referred to are electrophilic aromatic substitution, pericyclic, and base-catalyzed/nucleophilic.

(79) Schmidt, H.-W.; Schipfer, R.; Junek, H. *Liebigs Ann. Chem.* **1983**, 695.

(80) Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585.

(81) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819.

(82) The addition/decomposition product results from elimination of $TMSO^-$ from the initially formed addition intermediate, as shown below. An analogous step is proposed to occur in the Peterson olefination reaction (Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780).



which involve more than one class of reaction. The reaction sequences presented in this section illustrate this facet of the program.

An isoquinoline synthesis utilizing three classes of reactions is shown in example S4.1.[83] The first step, treated by the electrophilic heterocyclic module, is addition of the amine to the benzaldehyde to form the Schiff's base. Reduction with sodium borohydride provides amine **28** as predicted by the oxidative/reductive module in CAMEO.[5,6] Upon resubmission of intermediate **28** to the heterocyclic module, the program finds the substitution reaction with ethyl bromoacetate to give **29**. Structure **29**, along with an acid catalyst, is then resubmitted to the heterocyclic module for further processing. Here, the program predicts that the most viable reaction is an electrophilic aromatic substitution; consequently, this reaction is transferred to the EAS module for evaluation. Intramolecular EAS finally provides the only predicted and reported[83] product.

Synthesis of a polycyclic indole system is illustrated in example S4.2.[84] Here, intermediate **30** is predicted by the electrophilic heterocyclic module as the initial product. Upon submission to the pericyclic module, **30** is then predicted to undergo a [3,3] sigmatropic rearrangement to give **31**. Subsequent analysis of **31** by the heterocyclic module provides the observed indole via intramolecular addition/deamination. Thus, in this manner, the program can arrive at the product of a Fischer indole synthesis.

(83) Teitel, S.; Brossi, A. *J. Heterocycl. Chem.* **1970**, *7*, 1401.
(84) Bahadur, G. A.; Bailey, A. S.; Baldry, P. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1619.

V. Conclusion

The utility of the computer program CAMEO has been enhanced by the implementation of a package that treats reactions used in heterocycle synthesis. The heterocyclic package explicitly handles the major class of heterocycle-forming processes, i.e., electrophilic addition and substitution reaction under neutral and acidic conditions. The evaluation of these reactions required development of algorithms that consider nucleophile and electrophile reactivity, ring-size selectivity, and product formation. Regarding the last issue, a set of heterocyclic extended mechanistic steps was formulated for use in the construction of intermediates and products. Using a routine that assigns a mechanistic class to the input reactants, syntheses involving base-catalyzed and pericyclic reactions, electrophilic aromatic substitution, and radical or carbenoid intermediates can also be treated. Thus, the program is now capable of making predictions on the outcomes of a wide variety of heterocycle-forming processes.

Acknowledgment. Gratitude is expressed to the National Science Foundation for support of this work. M.G.B. also received fellowship support from Eastman Kodak, Inc.

Electroorganic Reactions. 31. Quinonemethide Radical-Anions and Dianions: Their Cathodic Generation and Reactivity

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Received August 31, 1987

The cathodic reactions of a number of relatively stable quinonemethides have been examined in detail by cyclic voltammetry, controlled potential coulometry, and rigorous product analysis following preparative-scale electrolyses. The results of cyclic voltammetric experiments differ in some respects from those of earlier polarographic work. The lifetimes of the electrogenerated radical-anions and dianions, in the absence of added electrophile, are governed by steric hindrance. Hindered intermediates are relatively long-lived yet hydrogenate in the presence of proton donor and alkylate in the presence of methyl iodide. Less hindered analogues efficiently and rapidly dimerize, at carbon, with concomitant protonation or O-methylation depending on added electrophile. The ambident cathodically generated nucleophiles alkylate at both carbon and oxygen, and the competition is crucially dependent on the cation (Bu_4N^+ or Li^+). Fuchsone **3** gives reduction products which vary with initial concentration and on the presence, or otherwise, of oxygen. Efficient reaction between oxygen and triarylmethyl radicals generated, e.g., from **3** has been demonstrated.

The electrochemistry of quinones received much early attention and provided some of the earliest examples of correlations between structure and redox potential. Despite this success, little attention has been paid to the electrochemical behavior of quinonemethides. The chemical reactions of quinonemethides are well understood and mostly involve the electrophilic character of the intermediates. Cathodic reduction brings about *umpolung*; the quinonemethides are converted into nucleophiles and bases, and we describe herein methods for the generation of such intermediates and preparative and electroanalytical experiments that illustrate their reactivity.

The quinonemethides chosen for study, compounds **1–6**, are relatively stable. Chemical reduction[1,2] and polarography[3] of compounds of this type have been investigated. There are also reports[4] of the preparative-scale electrolysis of quinonemethides, which indicate that hydrodimerization at the terminal carbon is a preferred reaction. Analysis of the polarographic results suggested[4b] that disproportionation of radical-anions might be significant. For less hindered and, consequently, more reactive quinone-

(1) Becker, H.-D.; Gustafsson, K. *J. Org. Chem.* **1976**, *41*, 214.
(2) Becker, H.-D.; Sanchez, D. *Tetrahedron Lett.* **1975**, 374.
(3) Krupicka, J.; Koutek, B.; Musil, L.; Pavlickova, L.; Soucek, M. *Collect. Czech. Chem. Commun.* **1981**, *46*, 861.
(4) (a) Richards, J. A.; Evans, D. H. *J. Electroanal. Chem. Interfacial Electrochem.* **1977**, *81*, 171. (b) Kudinova, L. I.; Volod'kin, A. A.; Ershov, V. V.; Prokofeva, T. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1978**, 1503.

0022-3263/88/1953-2520$01.50/0