methylurea.[20] 6-(Hydroxyamino)uracil (5) and 6-hydrazinouracil (6) were prepared[21] from condensation of 6-chlorobarbituric acid with hydroxylamine hydrochloride or hydrazine hydrate.

General Procedures for the Synthesis of Pyrido[2,3-*d*]pyrimidines 7–9 from the Reaction of Cyano Olefins 1–3 and 6-Aminouracil 4 or 6-(Hydroxyamino)uracil 5. A solution of 1.55 g (10 mmol) of **4a** and 4.62 g (30 mmol) of cyano olefin (**1a**) in 50 mL of 1-propanol was refluxed for 4 h. The reaction mixture was concentrated to half of its volume, cooled, and filtered. Recrystallization from ethanol gave light brown crystals of **7a** (2.82 g, 92%): mp 308–312 °C; ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 3 H), 3.42 (s, 3 H), 6.78–7.25 (m, 5 H); IR 3435, 3300, 2195, 1710 cm^{-1}; MS 307 (M^+).

Evaporation of the filtrate from **7a** followed by column chromatography on silica gel column (benzene) gave benzylmalononitrile (1.48 g, 95%): mp 90–92 °C (lit.[22] mp 91–92 °C); ^{1}H NMR ($CDCl_3$) δ 3.15 (d, 2 H), 3.70 (t, 1 H), 7.18 (m, 5 H); IR 2250 cm^{-1}; MS 153 (M^+).

General Procedure for the Synthesis of Pyrazolo[3,4-*d*]pyrimidine 10 from the Reaction of Cyano Olefins 1–3 and 6-Hydrazinouracil 6. A solution of 1.70 g (10 mmol) of **6a** and 4.62 g (30 mmol) of cyano olefin **1a** in 50 mL of 1-propanol was refluxed for 3 h. The reaction mixture was concentrated, cooled, and filtered. Recrystallization from ethanol gave **10a** (2.30 g, 90%): mp 258–259 °C; ^{1}H NMR (TFA) δ 2.95 (s, 3 H), 3.40 (s, 3 H), 6.75–7.20 (m, 5 H); IR 3220, 1700 cm^{-1}; MS 256 (M^+). Evaporation of the solvent from the filtrate of **7a** in vacuo and column chromatography on a silica gel column (benzene–petroleum ether) gave malononitrile (0.60 g, 90%) [mp 32–34 °C; bp 220 °C] and benzylmalononitrile (1.51 g, 97%): mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 3.15 (d, 2 H), 3.70 (t, 1 H), 7.18 (m, 5 H); IR 2250 cm^{-1}; MS 156 (M^+).

10b: yield 92%; mp 235–236 °C; ^{1}H NMR (TFA) δ 3.00 (s, 3 H), 3.45 (s, 3 H), 6.35–6.65 (m, 2 H), 7.25 (d, 1 H); IR 3225, 1705 cm^{-1}; MS 246 (M^+).

10c: yield 92%; mp 243–244 °C; ^{1}H NMR (TFA) δ 3.10 (s, 3 H), 3.50 (s, 3 H), 6.25–6.45 (m, 2 H), 7.15 (d, 1 H); IR 3220, 1705 cm^{-1}; MS 262 (M^+).

10d: yield 82%; mp 256–257 °C; ^{1}H NMR (TFA) δ 2.95 (s, 3 H), 6.80–7.25 (m, 5 H); IR 3250, 3125, 1700 cm^{-1}; MS 242 (M^+).

10e: yield 84%; mp 242–243 °C; ^{1}H NMR (TFA) δ 3.00 (s, 3 H), 6.30–6.45 (m, 2 H), 7.10 (d, 1 H); IR 3245, 3120, 1695 cm^{-1}; MS 232 (M^+).

10f: yield 87%; mp 257–258 °C; ^{1}H NMR (TFA) δ 3.05 (s, 3 H), 6.35–6.50 (m, 2 H), 7.15 (d, 1 H); IR 3245, 3115, 1700 cm^{-1}; MS 248 (M^+).

Synthesis of Pyrazolo[3,4-*d*]pyrimidine 10 from Reaction of 6 and 1 in Aprotic Solvent. A solution of 1.70 g (10 mmol) of **6a** and 3.08 g (20 mmol) of **1a** in 50 mL of dry DMF was heated at 125–130 °C for 2 h. The solvent was removed from the reaction mixture in vacuo, treated with water (75 mL), and filtered. Recrystallization of the crude compound from ethanol gave **10a** (2.18 g, 85%): mp 258–259 °C. Column chromatography of the residue obtained from the evaporation of the filtrate gave malononitrile (0.58 g, 88%), mp 32–34 °C, and benzylmalononitrile (1.48 g, 95%), mp 90–92 °C.

Acknowledgment. P.J.B. thanks the Council of Scientific and Industrial Research (India) for the award of a research associateship.

Registry No. **1a**, 2700-22-3; **1b**, 3237-22-7; **1c**, 28162-32-5; **2a**, 2025-40-3; **2b**, 23973-22-0; **2c**, 31330-51-5; **3a**, 709-79-5; **3b**, 3695-90-7; **3c**, 54688-95-8; **4a**, 6642-31-5; **4b**, 21236-97-5; **5a**, 42963-41-7; **5b**, 123506-39-8; **6a**, 123506-40-1; **6b**, 123506-41-2; **7a**, 95548-64-4; **7b**, 123506-42-3; **7c**, 123506-43-4; **7d**, 95548-68-8; **7e**, 123506-44-5; **7f**, 123506-45-6; **8a**, 123506-46-7; **8b**, 123506-47-8; **8c**, 123506-48-9; **8d**, 123506-49-0; **8e**, 123506-50-3; **8f**, 123506-51-4; **9a**, 123506-52-5; **9b**, 123506-53-6; **9c**, 123506-54-7; **9d**, 123506-55-8; **9e**, 123506-56-9; **9f**, 123506-57-0; **10a**, 35221-08-0; **10b**, 123506-58-1; **10c**, 123506-59-2; **10d**, 42748-33-4; **10e**, 123506-60-5; **10f**, 123506-61-6; $PhCH_2CH(CN)_2$, 1867-37-4.

Synthesis of 6*H*-Pyrrolo[1,2-*c*][1,2,3]triazoles and 5*H*-Pyrrolo[1,2-*d*]tetrazoles: Alkylation and Acylation of the Monoanions

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Thermal cyclization of 1-azido-2-penten-4-ynes and 4-azido-2-butenenitriles led to 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles and 5*H*-pyrrolo[1,2-*d*]tetrazoles, respectively, in good yields. Upon treatment with methyllithium these heterocyclic compounds gave the corresponding aromatic anions which can be alkylated with methyl iodide or acylated with ethyl chloroformate.

Unlike pentalene itself,[1] the corresponding pentalene dianion resulting from the addition of two electrons to the π-system is a stable material belonging to the class of aromatic compounds.[2] Ten general types of neutral heterocyclic systems have been recognized which are isoelectronic with the 10 π-electron system of the pentalenyl dianion.[3] Six of these can be represented by a covalent formulation, whereas only mesomeric betaine structures can be written for the four others. Several azapentalene anions have been prepared in solution as their lithium salts by deprotonation of the appropriate neutral compounds. The NMR spectra of these anions suggest that the negative charge is delocalized in a 10 π-electron system.[3,4] However little work has been devoted to the reactivity of these monoanions.[4,5]

In preliminary communications,[6] we reported that 1-azido-2-penten-4-ynes (**2**) can be thermally cyclized to a

(1) Block, R.; Marty, R. A.; de Mayo, P. *J. Am. Chem. Soc.* **1971**, *93*, 3071.

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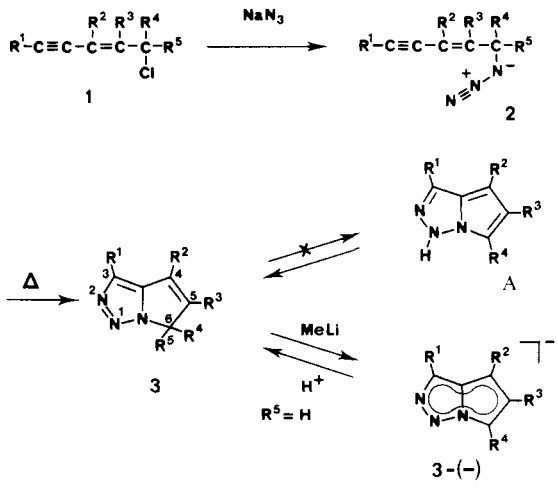
(4) For a review, see: Elguero, J.; Claramunt, R. M.; Summers, A. J. H. *Adv. Heterocycl. Chem.* **1978**, *22*, 183.

(5) (a) Albini, A.; Bettinetti, G. F.; Minoli, G. *J. Org. Chem.* **1983**, *48*, 1080. (b) Albini, A.; Bettinetti, G. F.; Minoli, G.; Fulle Soldi, T. *Chem. Lett.* **1984**, 1197.

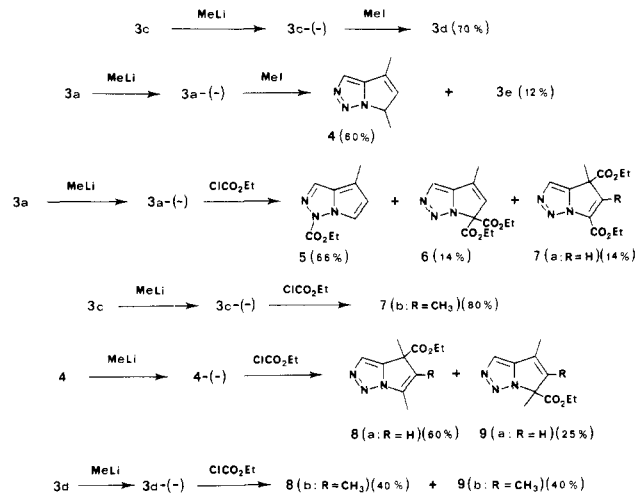
(6) (a) Dulcere, J. P.; Santelli, M.; Bertrand, M. *C. R. Hebd. Séances Acad. Sci. Série C* **1970**, *271*, 585. (b) Bertrand, M.; Dulcere, J. P.; Santelli, M. *Tetrahedron Lett.* **1977**, 1784.

0022-3263/90/1955-0571$02.50/0

Scheme I



Scheme II



a: $R^2 = CH_3$; $R^1 = R^3 = R^4 = R^5 = H$ b: $R^1 = R^2 = CH_3$; $R^3 = R^4 = R^5 = H$
c: $R^2 = R^3 = CH_3$; $R^1 = R^4 = R^5 = H$ d: $R^2 = R^3 = R^4 = CH_3$; $R^1 = R^5 = H$
e: $R^2 = R^4 = R^5 = CH_3$; $R^1 = R^3 = H$ f: $R^2R^3 = -(CH_2)_4-$; $R^4 = CH_3$; $R^1 = R^5 = H$

new class of azapentalene derivatives, the 6*H*-pyrrolo[1,2-*c*][1,2,3]triazoles (**3**). We describe here the extension of the scope of this reaction to the preparation of 5*H*-pyrrolo[1,2-*d*]tetrazoles (**15**) by the thermal cyclization of 4-azido-2-butenenitriles (**14**). The alkylation and the acylation of the 10 π-electron monoanions of **3** and **15** should offer a useful synthetic route to potentially bioactive heterocyclic compounds.[7]

Results

Azido enynes **2** are obtained in good yields by treatment of 1-chloro-2-penten-4-ynes **1**[8] with an aqueous solution of sodium azide. Heating a benzene solution of azides **2** results in the formation of the pyrrolotriazoles **3**. In this cycloaddition process the *Z* isomer of **2** is consumed, leaving behind unreacted *E* isomer[9] (azidoenyne **2e** cannot be isolated owing to its spontaneous cyclization to give **3e**).[10]

The anions of **3a** and **3c** were generated by reaction with methyllithium in THF at −20 °C.[13] The protonation of these anions regenerated starting **3a** and **3c**, respectively.

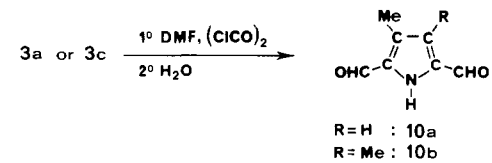
In particular, the formation of the tautomeric 1*H*-pyrrolo[1,2-*c*][1,2,3]triazoles A with a 10 π-electron conjugated system is not observed (Scheme I).[14] Likewise alkylation of these anions with methyl iodide occurs exclusively at the 6-position to give **4** and **3d**, respectively. A minor amount of the dimethylation produt **3e** is also observed from **3a** (Scheme II).

In contrast, acylation of the anions derived from **3** with ethyl chloroformate is less regioselective and takes place at the 1-, 4-, and 6-positions according to the substrate. The major product from **3a** is the N-acylated heterocycle **5**, which is particularly interesting, since a potentially aromatic structure is observed for the first time. This material undergoes spontaneous hydrolysis to regenerate **3a** and must be protected from moisture.

Evidence for aromaticity of **5** is found in its NMR spectrum, which shows the protons at C(3), C(5), and C(6) at relatively low field (δ 7.66, 7.57, and 6.32 ppm, respectively).

The anion derived from **3c** gives mainly the diacylated product **7b** resulting from reaction at both C(4) and C(6). The second acylation is undoubtedly facilitated by the increased acidity of the monoacyalted intermediate. Compounds **4** and **3d** are converted in a similar manner into mixtures of monoacylated products by substitution at C(6) and C(4), namely **8a**, **9a** and **8b**, **9b**, respectively.

An attempt to acylate triazole **3a** and **3c** with the Vilsmeier reagent[15] leads to formylation of the pyrrole ring with concomitant loss of nitrogen. The formation of dialdehyde **10** in this process surely results from electrophilic attack on the 1*H* tautomers A of the starting materials.



Isomeric mixtures of chlorobutenenitriles **12** and **13** are obtained from cyanohydrins **11**[16,17] by exposure to the

(7) Some dihydropyrrolotriazoles are known as herbicides, see: Abu-El-Haj, M. J.; McFarland, J. W. U.S. Pat. 4,002,636, and some dihydropyrrolotetrazoles have convulsant activities. See: (a) Rehavi, M.; Skolnick, Ph.; Paul, S. M. *Eur. J. Pharmacol.* **1982**, *78*, 353. (b) Squires, R. F.; Saederup, E.; Crawley, J. N.; Skolnick, Ph.; Paul, S. M. *Life Sci.* **1984**, *35*, 1439.

(8) (a) Heilbron, I. M.; Jones, E. R. H.; Lacey, R. N.; McCombie, J. T.; Raphael, R. *J. Chem. Soc.* **1945**, 77. (b) Santelli, M.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1973**, 2331.

(9) *trans,trans*-6-azidohexa-2,4-dienoate esters do not undergo intramolecular cycloaddition like the cis–trans isomers, see: Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1982**, *47*, 725.

(10) Although the intermolecular cycloaddition of an azide group to an acetylenic bond is a well-known process (see ref 11), few examples of intramolecular additions have been reported previously (see ref 12).

(11) For a review, see: (a) Lwowski, W. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 559–651. For recent examples, see: Vereshchagin, L. I.; Filippova, T. M.; Bol'shedvorskaya, R. L.; Gavrilov, L. D.; Pavlova, G. A. *Zh. Org. Khim.* **1984**, *20*, 142; *Chem. Abstr.* **1984**, *100*, 174738*v*.

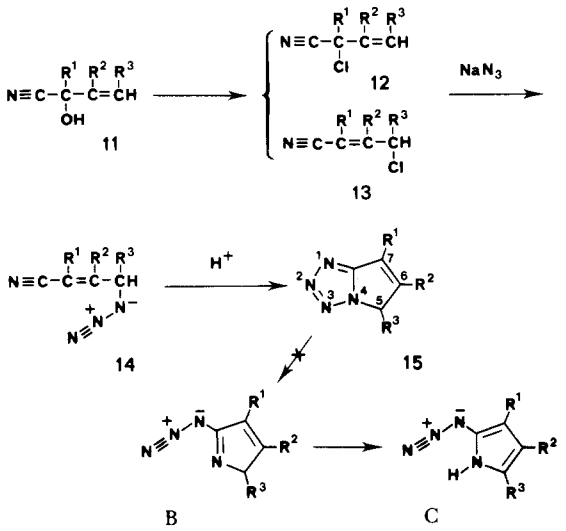
(12) (a) Fusco, R.; Garanti, L.; Zecchi, G. *J. Org. Chem.* **1975**, *40*, 1906. (b) Padwa, A. *Ang. Chem., Int. Ed. Engl.* **1976**, *15*, 123. (c) Davies, D.; Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2539. (d) Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2544.

(13) Anions are obtained by use of methyllithium at low temperature; butyllithium adds to the 5-position.

(14) The presence of two adjacent heteroatoms, each contributing a doublet to the π-system, is energetically unfavorable; see ref 4 and (a) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic Press: New York, 1976; p 266. (b) Faure, R.; Vincent, E. J.; Claramunt, R. M.; Fabrega, J. M.; Elguero, J. *Tetrahedron* **1976**, *32*, 341.

(15) Stadler, P. A. *Helv. Chim. Acta* **1978**, *61*, 1675.

Scheme III

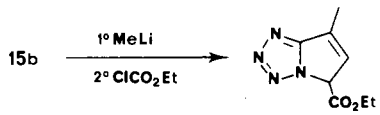


a: $R^1 = R^2 = R^3 = H$ **b**: $R^1 = CH_3$; $R^2 = R^3 = H$
c: $R^2 = CH_3$; $R^1 = R^3 = H$ **d**: $R^3 = CH_3$; $R^1 = R^2 = H$
e: $R^1 = R^2 = CH_3$; $R^3 = H$

Vilsmeier reagent.[15,18] Substitution with sodium azide occurs in good yield (80–85%) to give 4-azido-2-butenenitriles **14**. Azides add with more difficulty to nitriles than to olefins or acetylenes.[11a,19] In general, unactivated nitriles react with azides only when the two functions are incorporated into the same molecule,[20] and acid catalysis is necessary for the cycloaddition.[21] Thus, heating **14b,c,e** in the presence of chlorosulfonic acid proceeds smoothly to the pyrrolotetrazoles **15b,c,e**. These compounds constitute a new class of fused-ring heterocycles.[22] Azidonitriles **14a** (*E*:*Z* = 7:3) and **14d** (*E* isomer only) do not lead to the corresponding pyrrolotetrazoles, probably because of their unfavorable stereochemistry.

In the case of **15**, an azidoazole–azolotetrazole isomerization is possible.[4,23,24] Thus, the initial cycloadducts 5*H*-pyrrolo[1,2-*d*]tetrazoles could, in principle, equilibrate with the alternate open-chain valence tautomers 2-azidoisopyrroles B which could in turn undergo a favored tautomerism to 2-azidopyrroles C (Scheme III). In general the tendency for the formation of tetrazoles fused to a five-membered heterocycle from an azidoazole is low.[23] However, pyrrolotetrazoles **15** exhibit good thermal stability.[25]

Treatment of **15b** by NaH in DMSO leads to the corresponding anion which has been examined by proton and carbon NMR. This data is consistent with an aromatic structure, particularly the deshielded H-C(5) proton at 6.6 ppm and the C(5) carbon at 90.5 ppm in addition to the other ring carbons at 146.8 and 115 ppm. Interestingly acylation of this anion occurs exclusively at the C(5) position.



In conclusion, the cyclization of azido enynes or azidobutenenitriles respectively offers an efficient synthesis of pyrrolotriazoles or pyrrolotetrazoles. The easy formation of corresponding anions allows the preparation of several substituted derivatives.

Experimental Section

General Methods. ^1H NMR spectra were determined on Varian EM 360 or Varian XL 200 spectrometers and were recorded for $CDCl_3$ (or CCl_4) solutions containing Me_4Si as the internal Standard. ^{13}C NMR spectra of $CDCl_3$ solutions were recorded on a Varian XL 200 (50.309 MHz) spectrometer with Me_4Si as the internal standard. Assignments were confirmed by *J*-modulated spin echo. Mass spectra were obtained on a Varian MAT 311 mass spectrometer. Melting points are uncorrected. All reactions were carried out in an argon atmosphere.

Materials. 1-Chloro-2-penten-4-ynes (1) were prepared according to the reported method.[8b] Cyanhydrins **11a,b,c,e** were prepared by addition of cyanide anion to conjugated ethylenic aldehydes or ketones;[16] cyanhydrin **11d** was obtained by hydrolysis of the trimethylsilyl derivative.[17] Yields were as follows: 2-hydroxy-3-butenenitrile (**11a**), 61%; 2-hydroxy-2-methyl-3-butenenitrile (**11b**), 50%; 2-hydroxy-3-methyl-3-butenenitrile (**11c**), 88%; 2-hydroxy-3-pentenenitrile (**11d**), 92%; 2-hydroxy-2,3-dimethyl-3-butenenitrile (**11e**), 20%.

General Procedure for the Preparation of 6*H*-Pyrrolo[1,2-*c*][1,2,3]triazoles (3). Sodium azide (8.45 g, 130 mmol) was dissolved in water (20 mL) and 1-chloro-2-penten-3-ynes (1) were added (50 mmol). The mixture was stirred for 24 h. The azido enynes **2** were extracted by pentane. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude azido enynes were dissolved in benzene (500 mL). After refluxing (5 h), the solution was concentrated under reduced pressure to yield the crude triazole. Pure triazoles **3** were isolated by recrystallization from chloroform–pentane (1/4) or by chromatography on silica gel.

4-Methyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (3a). General procedure with 1-chloro-3-methyl-2-penten-4-yne (**1a**) (5.72 g): The benzene solution of the crude azido enyne (**2a**) was refluxed 4 h to give **3a** (4.35 g, 72%): mp 73 °C, picrate mp 128 °C; IR ($CDCl_3$) 1615, 815 cm^{-1}; ^1H NMR δ 7.40 (1, s), 6.25 (1, m, $W_{1/2}$ = 4 Hz), 4.73 (2, m, $W_{1/2}$ = 6 Hz), 2.13 (3, d, J = 2 Hz); ^{13}C NMR δ 146.7 (s), 129.7 (s), 128.4 (d), 122.4 (d), 51.1 (t), 13.3 (q); mass spectrum, *m/e* 122 (5), 121 (57), 93 (74), 67 (24), 66 (100), 65 (61), 40 (45), 39 (48); HRMS calcd for $C_6H_7N_3$ 121.0640, found 121.0636.

3,4-Dimethyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (3b). General procedure with 1-chloro-3-methyl-2-hexen-4-yne (**1b**) (6.42 g): The benzene solution of the crude azido enyne (**2b**) was refluxed 5

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(19) For reviews, see: (a) L'Abbé, G. *Chem. Rev.* **1969**, *69*, 345. (b) Lwowski, W. *The Chemistry of Azido Group*; Patai, S., Ed.; Wiley: New York, 1971; p 531.

(20) For examples of intermolecular cycloadditions, see: (a) Carpenter, W. R. *J. Org. Chem.* **1962**, *27*, 2085. (b) Krayushkin, M. M.; Beskopyl'nyi, A. M.; Zlotin, S. G.; Stashina, G. A.; Zhulin, V. M. *Dokl. Akad. Nauk SSSR* **1981**, *259*, 370; *Chem. Abstr.* **1981**, *95*, 150549*m*.

(21) (a) von Kereszty, Wolf, German Patent 611,692; *Chem. Abstr.* **1935**, *29*, 5994[9]. (b) Smith, P. A. S.; Clegg, J. M.; Hall, J. H. *J. Org. Chem.* **1958**, *23*, 524. (c) Volovenko, Yu. M.; Babichev, F. S. *Khim. Geterot. Soedin.* **1977**, 577; *Chem. Abstr.* **1977**, *87*, 68254*n*. (d) Doyle, M. P.; Whitefleet, J. L.; Bosch, R. J. *J. Org. Chem.* **1979**, *44*, 2923.

(22) Butler, R. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 323.

(23) For a review, see: Tisler, M. *Synthesis* **1973**, 123.

(24) (a) Claramunt, R. M.; Elguero, J.; Fruchier, A. Nye, M. J. *Afinidad* **1977**, *34*, 545; *Chem. Abstr.* **1979**, *90*, 203258*w*. (b) Butler, R. N.; McEvoy, T.; Alcalde, E.; Claramunt, R. M.; Elguero, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2886. (c) Olivella, S.; Vilarrasa J. *J. Heterocycl. Chem.* **1979**, 685. (d) Alcalde, E.; Elguero, J. *Chem. Scr.* **1984**, *23*, 195. (e) Gorini, J. A. C.; Farras, J.; Felix, M.; Olivella, S.; Solé, A.; Vilarrasa, J. *J. Chem. Soc., Chem. Commun.* **1986**, 959.

(25) For a discussion of the influence of the electronegativity of the atoms of the five-membered heterocyclic ring on the ability of the azide to cyclize, see ref 4 and Reynolds, G. A.; VanAllan, *J. A.*; Tinker, J. F. *J. Org. Chem.* **1959**, *24*, 1205.

h to give **3b** (oil), purified by chromatography on silica gel (ether–pentane) (5.94 g, 88%): IR 1615, 815 cm^{-1}; ^1H NMR (CCl_4) δ 6.15 (1, m, $W_{1/2}$ = 5 Hz), 4.73 (2, m, $W_{1/2}$ = 8 Hz), 2.36 (3, s), 2.16 (3, d, J = 2 Hz). Anal. Calcd for $C_7H_9N_3$: C, 62.22; H, 6.67; N, 31.11. Found: C, 62.40; H, 6.72; N, 30.89.

4,5-Dimethyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (3c). General procedure with 1-chloro-2,3-dimethyl-2-penten-4-yne (**1c**) (6.42 g): The benzene solution of crude **2c** was refluxed 1.5 h to give **3c** (5.26 g, 78%): mp 101 °C; picrate mp 132 °C; IR ($CDCl_3$) 1615, 815 cm^{-1}; ^1H NMR δ 7.28 (1, s), 4.63 (2, br s), 2.05 (6, br s); ^{13}C NMR δ 147.8 (s), 138.4 (s), 122.2 (s), 121.3 (d $^1J_{CH}$ = 195.3 Hz), 12.2 (q), 10.4 (q); mass spectrum, m/e 136 (8), 135 (73), 107 (55), 106 (100), 79 (83), 77 (38), 65 (40), 39 (43); HRMS calcd for $C_7H_9N_3$ 135.0796, found 135.0802.

4,5,6-Trimethyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (3d). General procedure with 2-chloro-3,4-dimethyl-3-hexene-5-yne (**1d**) (7.12 g): The benzene solution of crude **2d** was refluxed 8 h to give **3d** as an oil, purified by chromatography on silica gel (ether–pentane) (5.21 g, 70%): picrate mp 138 °C; IR ($CDCl_3$) 1615, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (1, s), 4.60 (1, q, J = 7 Hz), 2.0 (6, m), 1.58 (3, d, J = 7 Hz). Anal. Calcd for $C_8H_{11}N_3$: C, 64.43; H, 7.38; N, 28.19. Found: C, 64.54; H, 7.25; N, 28.24.

4,6,6-Trimethyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (3e). General procedure with 2-chloro-2,4-dimethyl-3-hexen-5-yne (**1e**) (7.12 g): Crude azido enyne **2e** could not be isolated; spontaneous cyclization occured to give **3e** (6.70 g, 90%): bp 70 °C (1 Torr); picrate mp 142 °C; IR 1615, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4 (1, s), 6.4 (1, q, J = 1.8 Hz), 2.11 (3, d, J = 1.8 Hz), 1.61 (6, s). Anal. Calcd for $C_8H_{11}N_3$: C, 64.43; H, 7.38; N, 28.19. Found: C, 64.58; H, 7.30; N, 28.11.

6-Methyl-4,5-tetramethylene-6*H*-pyrrolo[1,2-*c*][1,2,3]-triazole (3f). General procedure with **1f** (8.42 g): The benzene solution of crude **2f** was refluxed 5 h to give **3f** as an oil, purified by chromatography on silica gel (ether-pentane) (8.05 g, 92%): picrate mp 149 °C; IR 1615, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ (7.38 1, s), 4.76 (1, q, J = 7 Hz), 2.33 (4, m), 1.76 (4, m), 1.6 (3, d, J = 7 Hz). Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.57; H, 7.43; N, 24.00. Found: C, 68.49; H, 7.40;, N, 24.12.

General Procedure for the Alkylation or the Acylation of Triazoles or Tetrazoles. To a stirred solution of the heterocycle (10 mmol) in anhydrous THF (25 mL), cooled to −60 °C was added methyllithium (12 mmol in ether). The solution was allowed to warm at −20 °C and stirred for 1 h. The solution was cooled to −60 °C, and methyl iodide (2.13 g, 15 mmol) or ethyl chloroformate (1.63 g, 15 mmol) was added. After 4 h of stirring, the mixture was poured into ice containing ether. After separation of layers, the aqueous phase was extracted with ether, and the combined organic layers were washed with brine and dried ($MgSO_4$). The solution was concentrated under reduced pressure, and the crude products were purified by chromatography on silica gel (ether–pentane).

Methylation of 3a. Alkylation of **3a** (1.21 g) was performed with methyl iodide according to the general procedure. Two products were separated by chromatography on silica gel, **3e** (12%) and **4,6-dimethyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (4)** (60%): IR ($CDCl_3$) 1615, 810 cm^{-1}; ^1H NMR δ 7.40 (1, s), 6.22 (1, br s), 4.92 (1, q, J = 7 Hz), 2.15 (3, d, J = 1 Hz), 1.61 (3, d, J = 7 Hz). Anal. Calcd for $C_7h_9N_3$: C, 62.22; H, 6.67; N, 31.11. Found: C, 62.01; H, 6.77; N, 31.22.

Methylation of 3c. Alkylation of **3c** (1.35 g) by methyl iodide led to **3d** (65% yield).

Acylation of 3a. Acylation of **3a** (1.21 g) by ethyl chloroformate (1.41 g, 13 mmol) led to a mixture of **1-(ethoxycarbonyl)-4-methyl-1*H*-pyrrolo[1,2-*c*][1,2,3]triazole (5)** (66%), **6,6-bis(ethoxycarbonyl)-4-methyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (6)** (14%), and **4,6-bis(ethoxycarbonyl)-4-methyl-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (7a)** (14%). Compound **5** showed: IR ($CDCl_3$) 1730, 880, 860 cm^{-1}; ^1H NMR δ 7.66 (1, s), 7.57 (1, d, J = 2.4 Hz), 6.32 (1, d, J = 2.4 Hz), 4.52 (2, q, J = 7.2 Hz), 2.27 (3, s), 1.47 (3, t, J = 7.2 Hz). Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.96; H, 5.70; N, 21.76. Found: C, 55.78; H, 5.60; N, 21.86. Compound **6** showed: mp 94 °C (chloroform–pentane); IR (CCl_4) 1730, 860 cm^{-1}; ^1H NMR (CCl_4) δ 7.32 (1, s), 6.24 (1, br s), 4.24 (2, q, J = 7.2 Hz), 2.21 (3, br s), 1.33 (3, t, J = 7.2 Hz); ^{13}C NMR δ 162.9 (s) (2 C), 145.7 (s), 132.2 (s), 129.6 (d), 123.3 (d), 116.0 (s), 63.8 (t) (2 C), 13.9 (q) (2 C), 13.2 (q). Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.34; H, 5.66; N, 15.85. Found: 54.46; H, 5.59; N, 15.77. Compound **7a** showed: IR (CCl_4) 1770, 1685, 855 cm^{-1}; ^1H NMR (CCl_4) δ 8.07 (1, s), 7.09 (1, s), 4.58 (2, q, J = 7.2 Hz), 4.33 (2, q, J = 7.2 Hz), 2.25 (3, s), 1.50 (3, t, J = 7.2 Hz), 1.38 (3, t, J = 7.2 Hz); ^{13}C NMR δ 159.6 (s), 147.9 (s), 134.6 (s), 125.7 (d), 110.8 (d), 105.4 (s), 101.5 (s), 66.5 (t), 59.8 (t), 14.7 (q), 14.1 (q), 11.5 (q); mass spectrum, m/e 265 (49), 193 (22), 165 (37), 119 (100), 92 (63); HRMS calcd for $C_{12}H_{15}N_3O_4$ 265.1062, found 265.1040.

Acylation of 3c. Acylation of **3c** (1.35 g) by ethyl chloroformate (2.39 g, 22 mmol) led to **4,6-bis(ethoxycarbonyl)-4,5-dimethyl-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (7b)** (80% yield): IR ($CDCl_3$) 1765, 1660 cm^{-1}; ^1H NMR δ 8.0 (1, s), 4.61 (2, q, J = 7.2 Hz), 4.39 (2, q, J = 7.2 Hz), 2.43 (3, s), 2.17 (3, s), 1.52 (3, t, J = 7.2 Hz), 1.42 (3, t, J = 7.2 Hz). Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.09; N, 15.05. Found: C, 56.06; H, 6.18; N, 14.94.

Acylation of 4. Acylation of **4** (1.35 g) by ethyl chloroformate (1.42 g, 15 mmol) led to **4-(ethoxycarbonyl)-4,6-dimethyl-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (8a)** (60%) and **6-(ethoxycarbonyl)-4,6-dimethyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (9a)** (25%). Compound **8a** showed: IR ($CDCl_3$) 1750, 820 cm^{-1}; ^1H NMR δ 7.65 (1, s), 6.00 (1, s), 4.41 (2, q, J = 7.2 Hz), 2.48 (3, s), 2.20 (3, s), 1.43 (3, t, J = 7.2 Hz); ^{13}C NMR δ 151.6 (s), 134.4 (d), 128.5 (s), 126.3 (s), 116.0 (d), 106.6 (s), 64.5 (t), 14.3 (q), 14.0 (q), 11.1 (q). Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.97; H, 6.28; N, 20.29. Found: C, 57.88; H, 6.36; N, 20.34. Compound **9a** showed: IR (CCl_4) 1740, 860 cm^{-1}; ^1H NMR (CCl_4) δ 7.31 (1, s), 6.22 (1, q, J = 1.8 Hz), 4.14 (2, q, J = 7.2 Hz), 2.15 (3, d, J = 1.8 Hz), 1.82 (3, s), 1.21 (3, t, J = 7.2 Hz). Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.97; H, 6.28; N, 20.29. Found: C, 57.84; H, 6.30; N, 20.38.

Acylation of 3d. Acylation of **3d** (1.49 g) led to **4-(ethoxycarbonyl)-4,5,6-trimethyl-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (8b)** (40%) and **6-(ethoxycarbonyl)-4,5,6-trimethyl-6*H*-pyrrolo[1,2-*c*][1,2,3]triazole (9b)** (40%). Compound **8b** showed: IR (film) 1760, 1250 cm^{-1}; ^1H NMR (CCl_4) δ 7.47 (1, s), 4.34 (2, q, J = 7.2 Hz), 2.37 (3, s), 2.10 (3, s), 2.00 (3, s), 1.42 (3, t, J = 7.2 Hz); ^{13}C NMR δ 152.0 (s), 134.3 (d), 127.5 (s), 124.5 (s), 122.2 (s), 105.6 (s), 64.5 (t), 14.4 (q), 12.1 (q), 9.7 (q), 9.6 (q). Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.72; H, 6.79; N, 19.00. Found: C, 59.63; H, 6.84; N, 18,89. Compound **9b** showed: IR (film) 1760, 1260 cm^{-1}; ^1H NMR (CCl_4) δ 7.23 (1, br s), 4.10 (3, q, J = 7.2 Hz), 2.07 (3, d, J = 1.4 Hz), 1.95 (3, s), 1.79 (s), 1.17 (3, t, J = 7.2 Hz). Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.72; H, 6.79; N, 19.00. Found: C, 59.65; H, 6.76; N, 19.08.

Formylation of 3a and 3c. Vilsmeier salt (28.5 mmol)[15] in anhydrous CH_2Cl_2 (20 mL) was cooled and stirred at 0 °C. Triazole **3a** or **3c** (5 mmol) in anhydrous CH_2Cl_2 (30 mL) was added and stirred for 14 h. The reaction mixture was poured into ice and extracted with ether. The combined organic fractions were washed with brine and dried ($MgSO_4$). After concentration in vacuo, the crude product was recrystallized from chloroform–pentane to give **10a** (35% yield) [mp 83 °C; IR (CCl_4) 3300, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.56 (1, s), 9.39 (1, s), 6.53 (1, s), 2.3 (3, s); ^{13}C NMR δ 181.3 (d), 180.4 (d), 134.7 (s), 132.5 (s), 130.9 (s), 120.5 (d), 10.6 (q). Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.11; N, 10.21. Found: C, 61.36; H, 5.05; N, 10.27] or **10b** (30% yield): mp 137–138 °C; IR (CCl_4) 1750, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.75 (2, s), 2.31 (6, s); ^{13}C NMR δ 180.3 (d), 131.9 (s), 129.7 (s), 8.3 (q). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.60; H, 5.85; N, 9.21.

General Procedure for the Preparation of Chlorobutenenitriles (12 or 13). Vilsmeier salt (40 mmol)[15,18] in anhydrous acetonitrile (30 mL) was cooled to −20 °C and stirred. Cyanhydrin **11** (20 mmol) in anhydrous acetonitrile (20 mL) was slowly added. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was poured into ice and extracted with pentane. The layers were separated, and the aqueous fraction was extracted with pentane. The combined organic fractions were washed with brine and dried ($MgSO_4$). Concentration in vacuo and purification by chromatography on silica gel afforded **12** or **13**. **2-Chloro-3-butenenitrile (12a)** (53% yield): IR (film) cm^{-1}; ^1H NMR (CCl_4) δ 5.7–4.83 (3, m). **4-Chloro-2-methyl-2-butenenitrile (13b)** (57% yield): IR (film) 2220 cm^{-1}; ^1H NMR (CCl_4) δ 5.97 (1, t, J = 7.2 Hz), 4.03 (2, d, J = 7.2 Hz), 1.96 (3, br s). **2-Chloro-3-methyl-3-butenenitrile (12c)** (50% yield): IR (film) 2245, 925 cm^{-1}; ^1H NMR

(CCl_4) δ 5.33 (1, br s), 5.13 (1, br s), 4.92 (1, br s), 1.97 (3, br s); ^{13}C NMR δ 137.0 (s), 118.8 (t), 115.4 (s), 46.9 (d), 18.1 (q). **4-Chloro-3-methyl-2-butenenitrile (13c)** (25% yield): IR (neat) 2225 cm^{-1}; ^1H NMR (CCl_4) δ 5.30 (1, s), 3.90 (2, s), 2.04 (3, s). ***trans*-4-Chloro-2-pentenenitrile (13d)** (50% yield): IR (film) 2215 cm^{-1}; ^1H NMR (CCl_4) δ 6.37 (1, dd, J = 16, 6.2 Hz), 5.57 (1, d, J = 16 Hz), 4.53 (1, quint, J = 6.2 Hz), 1.60 (3, d, J = 6.2 Hz); ^{13}C NMR δ 153.4 (d), 116.3 (s), 100.9 (d), 54.4 (d), 23.8 (q). **4-Chloro-2,3-dimethyl-2-butenenitrile (13e)** (45% yield): IR (film) 2215 cm^{-1}; ^1H NMR (CCl_4) δ *Z* isomer 4.16 (2, s), 1.93 (6, br s); *E* isomer 3.96 (2, s), 1.93 (6, br s).

General Procedure for 4-Azido-2-butenenitriles (14). The same procedure as for azidopentenynes **2** was used and the crude product was purified by chromatography on silica gel (ether–pentane). **4-Azido-2-butenenitrile (14a)** (82% yield) (mixture of *E*/*Z* isomers, 7:3): IR (film) 2220, 2100 cm^{-1}; *E* isomer ^1H NMR δ 6.63 (1, dt, J = 16.2, 4.65 Hz), 5.60 (1, dt, J = 16.2, 2 Hz), 4.00 (2, dd, J = 4.6, Hz, 2 Hz); ^{13}C NMR δ 147.3 (d), 116.5 (s), 102.0 (d), 51.3 (t); *Z* isomer ^1H NMR δ 6.46 (1, dt, J = 11, 5.5 Hz), 5.54 (1, dt, J = 11, 1.4 Hz), 4.10 (2, d, J = 6.4 Hz, d, J = 2.8 Hz); ^{13}C NMR δ 146.6 (d), 114.1 (s), 103.1 (d), 50.2 (t). **(*Z*)-4-Azido-2-methyl-2-butenenitrile (14b)** (85% yield): IR (film) 2210, 2090 cm^{-1}; ^1H NMR (CCl_4) δ 6.09 (1, t, J = 7.2 Hz), 3.99 (2, d, J = 7.2 Hz), 2.04 (3, br s). **4-Azido-3-methyl-2-butenenitrile (14c)** (80% yield) (72:28 mixture of *E*/*Z* isomers): IR 2225, 2120 cm^{-1}; ^1H NMR (CCl_4) δ *E* isomer 5.38 (1, br s), 3.93 (2, br s), 2.05 (3, br s); *Z* isomer 5.30 (1, br s), 4.06 (2, br s), 2.05 (3, br s). ***trans*-4-Azido-2-pentenenitrile (14d)** (80% yield): IR (film) 2225, 2150 cm^{-1}; ^1H NMR (CCl_4) δ 6.47 (1, d, J = 16, 5.5 Hz), 5.47 (1, d, J = 16 Hz), 4.10 (1, quint, J = 6 Hz), 1.33 (3, d, J = 6 Hz). **4-Azido-2,3-dimethyl-2-butenenitrile (14e)** (82% yield) (29:71 mixture of *E*/*Z* isomers): IR (film) 2210, 2100 cm^{-1}; ^1H NMR (CCl_4) δ *E* isomer 3.85 (2, s), 1.89 (6, br s); *Z* isomer 3.98 (2, s), 1.89 (6 br s).

General Procedure for Tetrazoles (15). A solution of azidobutenenitrile (**14**) (5 mmol) in chloroform (30 mL) was treated at room temperature with chlorosulfonic acid (1.16 g, 10 mmol). After 0.5 h of stirring, the mixture was washed with a saturated solution of $NaHCO_3$ and dried ($MgSO_4$). After concentration in vacuo, the crude product was recrystallized from chloroform–pentane (1:4).

7-Methyl-5*H*-pyrrolo[1,2-*d*]tetrazole (15b). General procedure with **14b** gives **15b** (0.61 g) (57% yield): mp 113 °C; IR ($CDCl_3$) 1520, 1460, 1245 cm^{-1}; ^1H NMR δ 6.65 (1, t, J = 7.2 Hz), 4.78 (2, d, J = 7.2 Hz), 2.30 (3, s); ^{13}C NMR δ 164.0 (s), 135.0 (d), 127.9 (s), 50.3 (t), 12.4 (q); mass spectrum, m/e 123 (12), 122 (100), 94 (24), 93 (15), 79 (35), 66 (60), 65 (64), 39 (83); HRMS calcd for $C_5H_6N_4$ 122.0592, found 122.0584.

6-Methyl-5*H*-pyrrolo[1,2-*d*]tetrazole (15c). General procedure with **14c** gives **15c** (0.61 g) (25% yield): mp 104 °C; IR ($CDCl_3$) 1530, 1460 cm^{-1}; ^1H NMR δ 6.50 (1, br s, $W_{1/2}$ = 4 Hz), 4.73 (2, br s), 2.28 (3, s); ^{13}C NMR δ 164.2 (s), 154.7 (s), 112.5 (d), 53.5 (t), 16.0 (q). Anal. Calcd for $C_5H_6N_4$: C, 49.18; H, 4.92; N, 45.90. Found: C, 49.06; H, 4.73; N, 46.04.

6,7-Dimethyl-5*H*-pyrrolo[1,2-*d*]tetrazole (15e). General procedure with **14e** gives **15e** (0.68 g) (73% yield): mp 95 °C; IR ($CDCl_3$) 1530, 1460 cm^{-1}; ^1H NMR δ 4.74 (2, s), 2.19 (6, br s); ^{13}C NMR δ 164.6 (s), 132.9 (s), 120.8 (s), 53.1 (t), 13.0 (q), 9.7 (q); mass spectrum, m/e 137 (12), 136 (95), 108 (26), 80 (31), 79 (100), 77 (32), 67 (30), 53 (30), 40 (66); HRMS calcd for $C_6H_8N_4$ 136.0749, found 136.0753.

Formation of the Anion of 15b. Sodium hydride (30 mg) was added to a solution of **8b** (150 mg) in DMSO-d_6 (3 mL) in a 10-mm NMR tube. The NMR spectra were recorded after 10 min: ^1H NMR δ 6.62 (1, m), 6.10 (1, m), 2.1 (3, br s); ^{13}C NMR δ 146.5 (s), 115.0 (d), 90.5 (d), 79.1 (s), 12.1 (q).

Acylation of 15b. Acylation of **15b** (1.22 g) by ethyl chloroformate (1.42 g, 15 mmol) led to **5-(ethoxycarbonyl)-7-methyl-5*H*-pyrrolo[1,2-*d*]tetrazole (16)** (76%): mp 58–59 °C (chloroform–pentane); IR (CCl_4) 1750, 1250 cm^{-1}; ^1H NMR δ 6.69 (1, d, J = 3.5 Hz), 6.20 (1, d, J = 3.5 Hz), 4.38 (2, J = 7.2 Hz), 2.19 (3, s), 1.38 (3, t, J = 7.2 Hz); ^{13}C NMR δ 165.7 (s), 147.3 (s), 127.7 (s), 120.9 (d), 102.2 (d), 65.1 (t), 14.0 (q), 10.7 (q); mass spectrum, m/e 195 (10), 194 (63), 168 (10), 150 (10), 143 (57), 122 (100), 93 (75), 67 (72), 41 (56); HRMS calcd for $C_8H_{10}N_4O_2$ 194.0803, found 194.0796.

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Registry No. **1a**, 123810-18-4; **1b**, 123810-19-5; **1c**, 123810-20-8; **1d**, 123810-21-9; **1e**, 123810-22-0; **1f**, 38264-11-8; **2a**, 64803-97-0; **2b**, 64803-99-2; **2c**, 64803-96-9; **2d**, 64803-98-1; **2e**, 123810-23-1; **2f**, 64804-00-8; **3a**, 64804-02-0; **3b**, 64804-04-2; **3c**, 64804-01-9; **3d**, 64804-03-1; **3e**, 30435-17-7; **3f**, 64804-05-3; **4**, 123810-24-2; **5**, 123810-25-3; **6**, 123810-26-4; **7a**, 123810-27-5; **7b**, 123810-28-6; **8a**, 123810-29-7; **8b**, 123810-31-1; **9a**, 123810-30-0; **9b**, 123810-32-2; **10a**, 90935-74-3; **10b**, 51952-99-9; **11a**, 5809-59-6; **11b**, 75819-97-5; **11c**, 22410-56-6; **11d**, 6812-26-6; **11e**, 4346-65-0; **12a**, 24253-31-4; **12c**, 123810-33-3; **13b**, 92089-38-8; **13c**, 4450-34-4; **13d**, 123810-34-4; (*Z*)-**13e**, 123810-35-5; (*E*)-**13e**, 26157-52-8; (*E*)-**14a**, 123810-36-6; (*Z*)-**14a**, 123810-37-7; (*Z*)-**14b**, 123810-38-8; (*E*)-**14c**, 123810-39-9; (*Z*)-**14c**, 123810-40-2; (*E*)-**14d**, 120990-04-7; (*E*)-**14e**, 123810-41-3; (*Z*)-**14e**, 123810-42-4; **15b**, 123810-43-5; **15b** (anion), 123810-46-8; **15c**, 123810-44-6; **15e**, 123810-45-7; **16**, 123834-20-8.

β-Lactams via α,β-Unsaturated Acid Chlorides: Intermediates for Carbapenem Antibiotics[1]

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Stereocontrolled synthesis of α-vinyl β-lactams and their transformation to convenient intermediates for PS-5, PS-6, asparenomycin, and thienamycin are described.

Introduction

The acid chloride–imine reaction has been used extensively to synthesize various substituted β-lactams.[2] Azidoacetyl chloride–imine cycloaddition, also known as the Bose reaction,[3] has been used as a pivotal synthetic

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