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1,3-Dimethyluracil (**1**), a versatile synthon for the synthesis of various heterocycles, reacted readily with 3-aminopyrazoles **2** in sodium ethoxide to give pyrazolo[1,5-*a*]pyrimidines **3**. Under similar conditions, 3-aminopyrazole C-nucleosides **4** and the synthon **1** gave a mixture of pyrazolo[1,5-*a*]pyrimidine C-nucleosides, which was separated on a silica gel column. Attempts to remove the protecting groups yielded pyranose derivative **10**. Another synthon 1,3-dimethyl-5-azauracil and 3-aminopyrazoles **12** gave pyrazolo[1,5-*a*]triazines **13**. In a similar reaction with 3-aminopyrazole C-nucleosides **4** gave the corresponding pyrazolo[1,5-*a*]triazine C-nucleosides **14** and **15**.

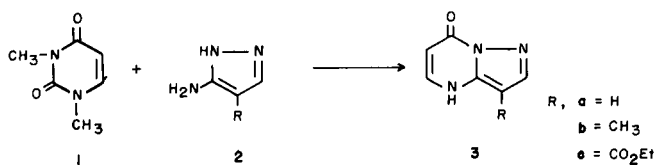
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Recently, 1,3-dimethyluracil (**1**) and its derivatives have been found to be useful synthons for the synthesis of various heterocycles [1-7]. In an addition-elimination reaction **1** can transfer an  $\alpha,\beta$ -unsaturated keto-moiety to incoming nucleophiles. We have utilized this type of reaction in the synthesis of 2'-deoxypseudoisocytidine in which 1,3-dimethyl-2'-deoxypseudouridine was treated with a nucleophile, guanidine [1,2]. By the similar reaction Hirota *et al.* [3] also converted 1,3-dimethylpseudouridine to pseudoisocytidine, which is a potent antileukemic agent [8,9]. This method circumvented the difficulties encountered in the synthesis of pseudoisocytidine. Recently we have also converted 1,3-dimethylacyclopseudouridine into acyclopseudoisocytidine in a similar reaction [10].

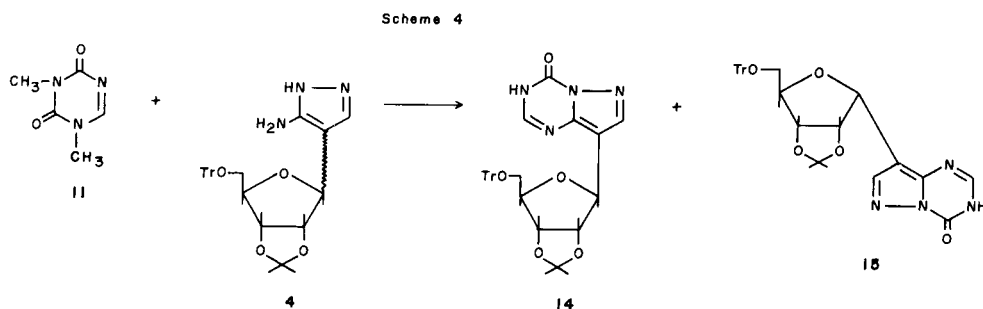
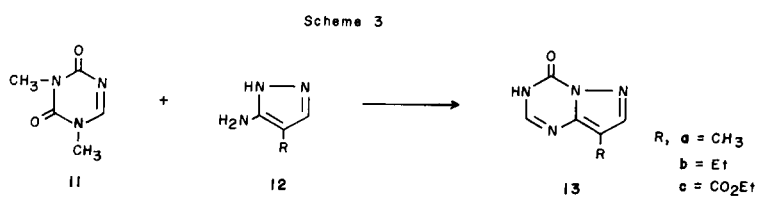
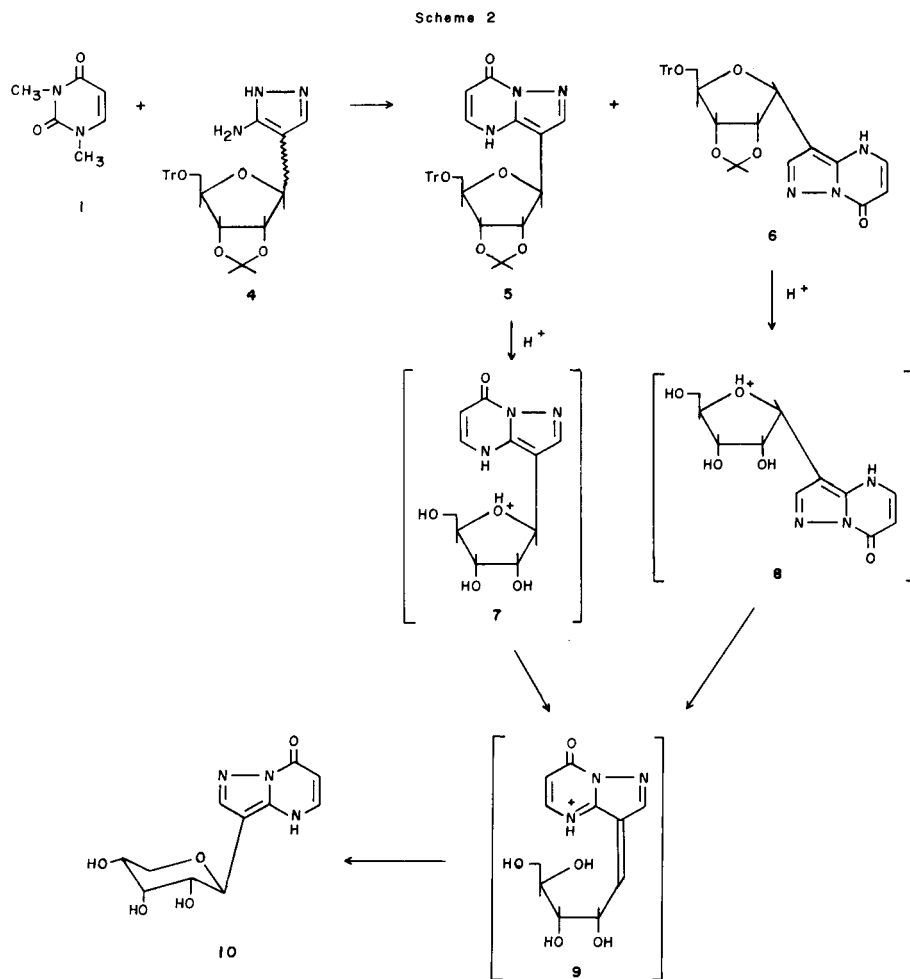
In previous works, however, simple nucleophiles such as guanidine [1-3], urea [3], thiourea [3], acetamides [4] except 1,3-dimethyl-6-aminouracil [4], have been used. This report deals with the utilization of 3-aminopyrazoles and their C-nucleosides derivatives as nucleophiles in the synthesis of pyrazolo[1,5-*a*]pyrimidines **3**, pyrazolo[1,5-*a*]triazines **13**, and their corresponding C-nucleosides. 3-Aminopyrazole may be viewed as a heterocycle with an amidine moiety incorporated into the ring system. In order to test the feasibility of the reaction, various 4-substituted 3-aminopyrazoles **2** were treated with 1,3-dimethyluracil (**1**) in sodium ethoxide solution (Scheme 1). 3-Substituted

reaction provided easy access to pyrazolo[1,5-*a*]pyrimidine system [11,12]. Furthermore, the reaction has also been demonstrated to be useful in the synthesis of pyrazolo[1,5-*a*]pyrimidine C-nucleosides **5** and **6** (Scheme 2). Thus, from the reaction of 3-aminopyrazole C-nucleosides **4** (an anomeric mixture) and 1,3-dimethyluracil (**1**), an anomeric mixture of pyrazolo[1,5-*a*]pyrimidine C-nucleosides **5** and **6** was obtained after silica gel column chromatography. Even if a single isomer of 3-aminopyrazole C-nucleoside was used, a mixture of  $\alpha$ - and  $\beta$ -anomers **5** and **6** was obtained due to the anomerization during the reaction, which is consistent with our previous observation [13,14]. The assignment of anomeric configuration of **5** and **6** was mainly based on the chemical shifts of the anomeric protons in which H-1' of the  $\beta$ -anomer appeared at higher field ( $\delta$  4.95) than that of the  $\alpha$ -anomer ( $\delta$  5.26). It should be mentioned that the differences of chemical shifts between the methyl groups ( $\Delta\delta$ ) for the  $\alpha$ - and  $\beta$ -anomer were both 0.24 ppm. Thus, the Imbach rule [15] does not apply for the assignment of **5** and **6**, which is often the cases with other "purine-like" C-nucleosides with large aromatic substitutions at 5'-position [16]. In order to obtain free nucleosides **5** and **6** were separately treated with 10% methanolic hydrogen chloride at room temperature. According to nmr spectra both **5** and **6** gave the same product **10**, in which the coupling constant of H1' and H2' ( $J_{1',2'}$ ) was 9.9 Hz. This result could only be accommodated by pyranose-form with  $\beta$ -configuration [17]. Furthermore, compound **10** showed three exchangeable doublets for three hydroxyl groups in deuterated dimethyl sulfoxide at 270 MHz, which confirmed the above assignment. Previously, we observed similar results ( $J_{1',2'} = 9.7$  Hz) during the deblocking of 3-amino-2*N*-carbamoyl-4-( $\beta$ -D-ribofuranosyl)pyrazole to free nucleosides [14]. The above results indicate that initially formed ribo-nucleosides **7** and **8** underwent the ring-opening reaction to **9**, which was recycled to give exclusively pyranose derivative **10**.

Scheme 1



pyrazolo[1,5-*a*]pyrimidine derivatives **3** were readily obtained by filtration of the resulting sodium salts followed by the neutralization of the aqueous solution. This simple



The general utility of this reaction was also demonstrated in the synthesis of pyrazolo[1,5-*a*]triazines **13** and its *C*-nucleosides **14**, and **15** with another heterocyclic synthon, 1,3-dimethyl-5-azauracil (**11**).

Previously we utilized the synthon for the ring transformation reaction from *S*-triazine to pyrimidines [18]. Aminopyrazoles **12** were reacted with 1,3-dimethyl-5-azauracil (**11**) in sodium ethoxide to afford pyrazolo[1,5-*a*]tria-

zines (**13**) (Scheme 3). Upon treatment of **11** with **4**, an anomeric mixture (1:1) of pyrazolo[1,5-*a*]triazine C-nucleosides **14** and **15** was obtained in fair yield (Scheme 4). The deblocked compounds of **14** and **15** have been previously reported [20].

Thus, the foregoing reactions of aminopyrazoles with 1,3-dimethyluracil and 1,3-dimethyl-5-azauracil have demonstrated the utility in the synthesis of pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]triazines. Furthermore, facile syntheses of hitherto unknown C-nucleosides **5**, **6**, and **10** have been achieved.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The <sup>1</sup>H nmr spectra were recorded on a JEOL FX90Q or FX270 fourier transform spectrometer. Tetramethylsilane was the internal standard for organic solvents and sodium 3-(trimethylsilyl)-1-propane-1-sulfonate (DSS) was the internal standard for deuterium oxide; chemical shifts are reported in parts per million ( $\delta$ ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), b (broad), m (multiplet). Ultraviolet spectra were recorded on a Bausch and Lomb Spectronic 2000 spectrometer. Thin-layer chromatography was performed on Uniplates purchased from Analtech Co. or Pre-coated tlc sheets (Silica gel 60) (F-254) by EM Laboratories, Inc. Elemental analysis was performed by Atlantic Microlab, Inc., Atlanta, GA.

### Pyrazolo[1,5-*a*]pyrimidin-7-one (**3a**).

A mixture of 1,3-dimethyluracil (**1**) (760 mg, 5.4 mmoles) and 3-aminopyrazole (**2a**) (322 mg, 4.0 mmoles) in 5 ml of sodium ethoxide solution (1 mole) was heated at 90-95° for one hour and then cooled in an ice-water bath. The resulting precipitate (400 mg) was dissolved in water (10 ml) and neutralization with acetic acid gave creamy colored crystals **3a** (330 mg, 61%), mp 239-240° (330-331° reported) [11]; uv:  $\lambda$  max 228 and 269 ( $\rho$ H 1), 227 and 268 ( $\rho$ H 7), 234, 239 (sh) and 313 (sh) ( $\rho$ H 12); <sup>1</sup>H nmr (dimethylsulfoxide-*d*<sub>6</sub>):  $\delta$  5.80 (d, 1, H-3,  $J_{2,3} = 2.0$  Hz), 5.94 (d, 1, H-5,  $J_{5,6} = 7.9$  Hz), 7.75 (d, 1, H-2), 8.47 (d, 1, H-6).

### 3-Methylpyrazolo[1,5-*a*]pyrimidin-7-one (**3b**).

A mixture of 1,3-dimethyluracil (**1**) (700 mg, 5 mmoles) and 3-amino-4-methylpyrazole (**2b**) (600 mg, 5.3 mmoles) in 7 ml of sodium ethoxide solution (1 mole) was heated at 95-100° for 2 hours and then cooled in an ice-water bath. The resulting white precipitate (650 mg) was dissolved in water (15 ml) and neutralized with acetic acid. The resulting white precipitate was filtered to collect **3b** (390 mg, 52%), mp 252-253°; uv:  $\lambda$  max 237 and 272 ( $\rho$ H 1), 237 and 273 ( $\rho$ H 7), 242, 247 (sh) and 315 (sh) ( $\rho$ H 12); <sup>1</sup>H nmr (dimethylsulfoxide-*d*<sub>6</sub>):  $\delta$  3.32 (s, 3, CH<sub>3</sub>), 5.84 (d, 1, H-5,  $J_{5,6} = 7.9$  Hz), 7.58 (s, 1, H-2), 8.36 (d, 1, H-6), 11.99 (b, 1, H-4, exchangeable).

Anal. Calcd. for C<sub>7</sub>H<sub>7</sub>N<sub>3</sub>O: C, 56.37; H, 4.70; N, 28.19. Found: C, 56.45; H, 4.74; N, 28.17.

### 3-Ethoxycarbonylpyrazolo[1,5-*a*]pyrimidin-7-one (**3c**).

A mixture of 1,3-dimethyluracil (**1**) (700 mg, 5 mmoles) and 3-amino-4-carboxypyrazole (**2c**) (780 mg, 5 mmoles) in 7 ml of sodium ethoxide solution (1 mole) was heated at 85-90° for one hour, and then cooled in an ice-water bath. The resulting precipitate was dissolved in water and neutralized with acetic acid. The resulting precipitate was filtered to collect **3c** (355 mg, 34%). mp 217-219°; <sup>1</sup>H nmr (dimethylsulfoxide-*d*<sub>6</sub>):  $\delta$  1.29 (t, 3, CH<sub>3</sub>, J = 7.0 Hz), 4.28 (q, 2, CH<sub>2</sub>), 6.15 (d, 1, H-5,  $J_{5,6} = 7.9$  Hz), 8.13 (s, 1, H-2), 8.57 (d, 1, H-6).

Anal. Calcd. for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.11; H, 4.37; N, 20.26.

### 3-( $\beta$ -D-2,3-O-Isopropylidene-5-O-tritylribofuranosyl-7-oxo-4H-pyrazolo[1,5-*a*]pyrimidine (**5**) and its $\alpha$ -Anomer (**6**).

A mixture of 1,3-dimethyluracil (1.12 g, 8 mmoles), 3-aminopyrazole C-nucleosides **4** (2.0 g, 4 mmoles, an  $\alpha,\beta$  mixture), sodium ethoxide (20 ml, 1 mole) and absolute ethanol (10 ml) was heated at 90° for 15 hours. After cooling the mixture was neutralized with acetic acid, which was filtered and the filtrate was evaporated to a syrup. Chloroform (30 ml) was added, triturated, filtered and the filtrate was evaporated to a syrup, which indicated two major spots on a thin-layer plate (chloroform/methanol = 20/1, R<sub>f</sub>  $\cong$  0.5). The mixture was separated on a silica gel column (30 inch) using a mixture of chloroform/methanol (50/1) as an eluent to give a slow moving compound  $\beta$ -isomer **5** (775 mg); <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  1.36 and 1.60 (s, 6, isopropylidene group), 3.25-3.40 (m, 2, H-5' and H-5''), 4.20-4.38 (m, 1, H-4'), 4.68 (dd, 2, H-2' and H-3'), 4.95 (m, 1, H-1'), a long range coupling with H-3' was noted), 5.93 (d, 1, H-5,  $J_{5,6} = 7.9$  Hz), 7.20-7.47 (m, 15, trityl), 7.62 (s, 1, H-2), 8.05 (d, 1, H-6).

Anal. Calcd. for C<sub>33</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub> + Methanol [19]: C, 70.22; H, 6.02; N, 7.22. Found: C, 70.40; H, 5.84; N, 7.40.

A fast moving compound  $\alpha$ -isomer **6** (530 mg) was also obtained from the same column; <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  1.34 and 1.58 (s, 6, isopropylidene group), 3.22-3.38 (m, H-5' and H-5''), 4.20-4.34 (m, 1, H-4'), 4.75-4.91 (m, 2, H-2' and H-3'), 5.26 (d, 1, H-1',  $J_{1',2'} = 2.4$  Hz), 5.99 (d, 1, H-5,  $J_{5,6} = 7.9$  Hz), 7.26-7.45 (m, 15, trityl), 7.70 (s, 1, H-2), 8.05 (d, 1, H-6).

Anal. Calcd. for C<sub>33</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub> + Methanol [19]: C, 70.22; H, 6.02; N, 7.22. Found: C, 69.96; H, 5.83; N, 7.37.

### 3-( $\beta$ -D-Ribopyranosyl)-7-oxo-4H-pyrazolo[1,5-*a*]pyrimidine (**10**). Method A (from **5**).

A mixture of **5** (500 mg) and methanolic hydrogen chloride (5 ml, 10%) was stirred for 30 minutes at room temperature during which colorless crystals were precipitated (170 mg, 70%), mp 177-178°; uv:  $\lambda$  max 231 (11,770) and 268 (4,490) ( $\rho$ H 1), 231 (11,880) and 268 (4,460) ( $\rho$ H 7), 238 (17,840), 243 (sh) (1,770) and 317 (sh) ( $\rho$ H 12); <sup>1</sup>H nmr (dimethylsulfoxide-*d*<sub>6</sub>):  $\delta$  3.41-3.55 (m, 4, H-2', H-4', H-5' and H-5''), 3.90 (m, 1, H-3'), 4.46 (d, 1, H-1',  $J_{1',2'} = 9.9$  Hz exchangeable), 4.54 (d, 1, OH, J = 8.6 Hz), 4.66 (d, 1, OH, J = 6.6 Hz, exchangeable), 4.79 (d, 1, OH, J = 3.3 Hz, exchangeable), 5.89 (d, 1, H-5,  $J_{5,6} = 7.9$  Hz), 7.30 (s, 1, H-4, exchangeable), 7.68 (s, 1, H-2), 8.40 (d, 1, H-6), 11.80 (b, 1, NH, exchangeable).

Anal. Calcd. for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.34; H, 4.91; N, 15.69.

### Method B (from **6**).

A mixture of **6** (500 mg) and 5 ml of methanolic hydrogen chloride (10%) was stirred for 2 hours at room temperature during which colorless crystals were precipitated (155 mg, 64%). This product was spectroscopically same as the compound from Method A.

### 8-Methyl-4-oxo-3H-pyrazolo[1,5-*a*]-1,3,5-triazine (**13a**).

A mixture of 1,3-dimethyl-5-azauracil (**11**) (846 mg, 6 mmoles), 3-amino-4-methylpyrazole (678 mg, 6 mmoles), 10 ml of sodium ethoxide solution (1 mole), and 5 ml of absolute ethanol was heated at 90-95° for 5 hours, and then cooled in an ice-water bath. The resulting precipitate was dissolved in water, neutralized with acetic acid, cooled in refrigerator, and then collected the resulting precipitate (0.58 g, 64%). This product was indistinguishable from an authentic sample [14].

### 8-Ethyl-4-oxo-3H-pyrazolo[1,5-*a*]-1,3,5-triazine (**13b**).

A mixture of 1,3-dimethyl-5-azauracil (**11**) (700 mg, 5 mmoles) and aminopyrazole **12b** (1.0 g, 9 mmoles) in sodium ethoxide solution (1 mole, 10 ml) was heated 95-100° for 15 hours. The mixture was cooled,

neutralized with acetic acid, evaporated to dryness. After addition of water (10 ml), the solution was stored in a refrigerator for a few hours and then the resulting precipitate was collected and washed with a small amount of methanol. An analytical sample was obtained from recrystallization from water, mp 273-277° dec; uv:  $\lambda$  max 265 (pH 1), 269 (pH 7) and 272 (pH 12); <sup>1</sup>H nmr (dimethylsulfoxide-d<sub>6</sub>):  $\delta$  1.20 (t, 3, CH<sub>3</sub>, J = 7.5 Hz), 2.59 (q, 2, CH<sub>2</sub>), 7.94 (s, 1, H-2), 7.99 (s, 1, H-7), 12.43 (b, 1, NH, exchangeable).

Anal. Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O: C, 51.22; H, 4.88; N, 34.15. Found: C, 51.37; H, 4.92; N, 34.14.

#### 8-Carboxy-4-oxo-3H-pyrazolo[1,5-a]-1,5-triazine (**13c**).

A mixture of 1,3-dimethyl-5-azauracil (**11**) (1.41 g, 10 mmoles), aminopyrazole **13c** (1.55 g, 10 mmoles), sodium ethoxide solution (1 mole, 15 ml) and absolute ethanol (10 ml) was refluxed for 15 hours. After heating the solvent was evacuated to a syrup, which was dissolved in water (30 ml), neutralized with diluted hydrochloric acid. The resulting precipitate was collected by filtration and recrystallized from 95% ethanol to give 0.89 g (43%), mp 276-277°; <sup>1</sup>H nmr (dimethylsulfoxide-d<sub>6</sub>):  $\delta$  1.29 (t, 3, CH<sub>3</sub>, J = 7 Hz), 4.28 (t, 2, CH<sub>2</sub>), 8.25 (s, 1, H-7), 8.36 (s, 1, H-2), 13.10 (b, 1, NH, exchangeable).

Anal. Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>4</sub>O<sub>3</sub>: C, 46.15; H, 3.85; N, 26.92. Found: C, 46.35; H, 3.79; N, 26.88.

#### 4-Oxo-3H-8-( $\alpha$ and $\beta$ -D-2,3-O-Isopropylidene-5-O-tritylribofuranosyl)pyrazolo[1,5-a]-1,3,5-triazine (**14** and **15**).

A mixture of 1,3-dimethyl-5-azauracil (700 mg, 5 mmoles) and aminopyrazole C-nucleosides **4** (1.5 g, 5 mmoles, anomeric mixture,  $\alpha/\beta$  = 55/45) in 10 ml of sodium ethoxide (1 mole) was heated at 90° for 15 hours. The mixture was then cooled at room temperature, neutralized carefully with acetic acid, and then evaporated to a syrup, which was separated on a silica gel column using chloroform/methanol (20:1) as an eluent to obtain  $\alpha,\beta$ -mixture **14** and **15** (820 mg). These products were indistinguishable from an authentic sample [14].

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