Chemistry of Heterocyclic Compounds, Vol. 44, No. 10, 2008

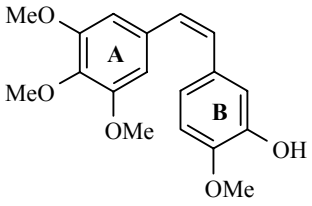
HETEROCYCLIC ANALOGS OF COMBRETASTATIN A-4

S. F. Vasilevsky[1], M. P. Davydova[1], and G. A. Tolstikov[2]

A novel route is proposed for the synthesis of heterocyclic analogs of the naturally occurring combretastatin A-4 based on the reaction of α-acetylenic ketones with polyfunctional nucleophiles (hydroxylamine, hydrazine, guanidine). Previously unknown combretastatin A-4 analogs with azole and azine bridges were obtained.

Keywords: acetylenes, combretastatin A-4, heterocyclization, homogeneous catalysis, cross-coupling.

Combretastatins are mitotic agents separated from the bark of the South African tree *Combretum Caffrum*. The most effective of them is combretastatin A-4 which has shown high cytotoxic activity towards a broad range of human tumors including many medicine resistant cell lines [1].



Combretastatin A-4

In recent years a key trend in the search for biologically active compounds in the combretastatin A-4 series is modification of its molecule through change of the *cis*-olefine bridge for a heterocyclic residue. Hence a targeted synthesis of combretastatin A-4 molecules including 5-membered nitrogen heterocycles (pyrazole, imidazole, oxazole) has been carried out and these show high antitumor activity [1]. The high antirheumatic activity discovered for the pyrimidine derivative TAS-202 infers that it may be used therapeutically [2].

However, the indicated analogs obtained demand either multistage syntheses (the oxazole and pyrazole derivatives) or an organometallic synthesis and absolute solvents (imidazole derivatives) [1]. The synthesis of the pyrimidine analog TAS-202 also involves 4 stages and the use of butyl lithium in absolute THF [2].

* Dedicated to Academician of the Russian Academy of Sciences B. A. Trofimov on his 70th jubilee.

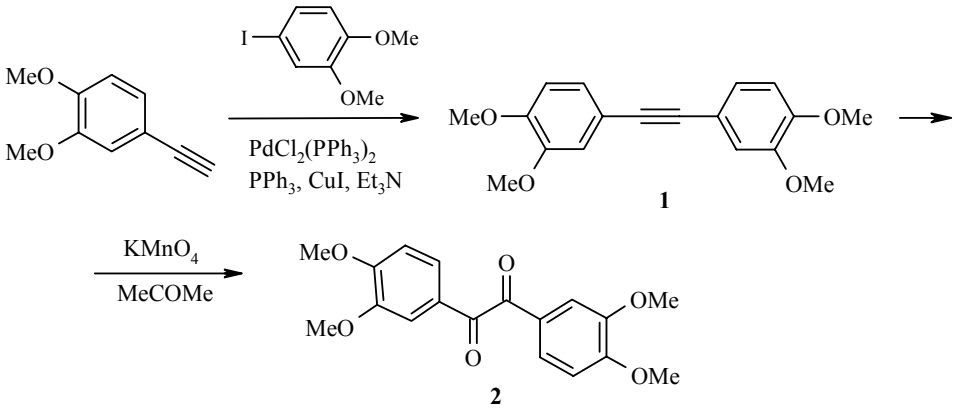
[1]Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, Novosibirsk 630090; e-mail: vasilev@kinetics.nsc.ru. [2]N. N. Vorozhtsov Institute for Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Novosibirsk 630090, e-mail: gtolstik@nioch.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1545-1549, October, 2008. Original article submitted May 28, 2008.

0009-3122/08/4410-1257©2008 Springer Science+Business Media, Inc.

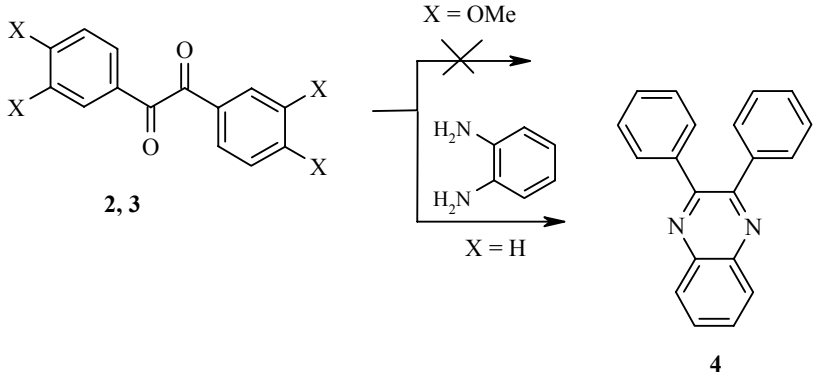
In this work we have studied the possibility of another route to formation of the heterocyclic fragments of combretastatin A-4 analogs based on acetylenic compounds or their modification products.

The key compound 1,2-diarylacetylene **1** was prepared by the method proposed by A. P. Rudenko and coworkers [3] (Scheme 1).

Scheme 1



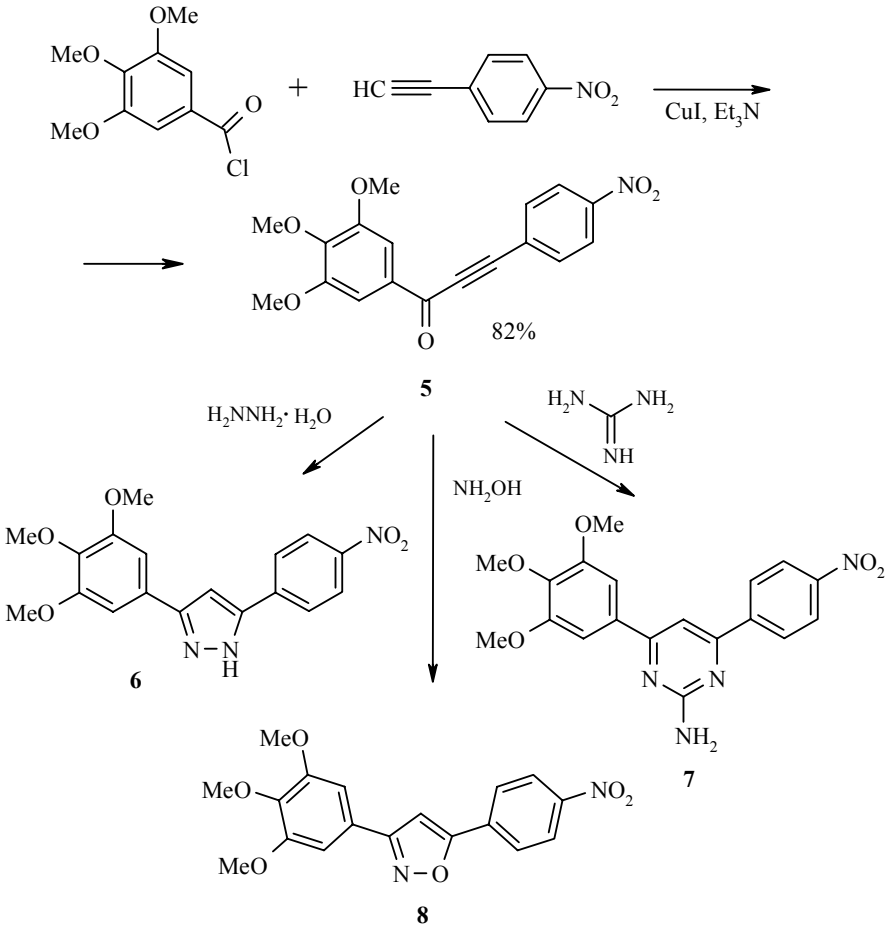
One of the proposed routes for synthesis of heterocyclic analogs of combretastatin A-4 involved reaction of diketone **2** with *o*-phenylenediamine. The dicarbonyl compound **2** was previously obtained by reaction of methylvanillin with potassium cyanide [4]. We have proposed a preparatively more convenient and ecologically acceptable method through oxidation of the diarylacetylene **1** using potassium permanganate in acetone to give the diketone **2** in 74% yield (Scheme 1). However, an attempt to synthesize the 1,4-diazine derivative by reaction of compound **2** with *o*-phenylenediamine was unsuccessful and this is likely connected with deactivation of the carbonyl groups by the OMe donor substituents in the aryl fragments. In fact, the benzil **3** and *o*-phenylenediamine gave a 60% yield of the 2,3-diphenylquinoxaline (**4**) (Scheme 2).



2 X = OMe, **3** X = H

Another variant of the synthesis of combretastatin analogs involves the use of aryl(arylethynyl)ketones with an activated triple bond. The target compound **5** was prepared in 82% yield by condensation of 3,4,5-trimethoxybenzoyl chloride with *p*-nitrophenylacetylene in the presence of CuI. The conjugated activated system gave the potential of carrying out a nucleophilic addition of polyfunctional nucleophiles (hydrazine hydrate, hydroxylamine, and guanidine) *via* heating the corresponding bases with the ketoacetylene to form the pyrazole **6** (56%), pyrimidine **7** (52%), or isoxazole derivative **8** (48%) (Scheme 3).

Thus aryl (arylethynyl) ketones are promising synthons which allow the addition of nitrogen-containing nucleophiles to the activated triple bond to form novel combretastatin A-4 analogs with azole and azine bridges.



EXPERIMENTAL

IR spectra were recorded on a Vector 22 spectrometer for KBr tablets. High resolution mass spectra were obtained on a Finnigan MAT model 8200 instrument (EI, 70 eV). ^{1}H NMR spectra were recorded on a Bruker AV-300 instrument (300 MHz). Chemical shifts were measured relative the residual undeuterated solvent signals: 7.24 ($CHCl_3$) or 2.50 ppm (DMSO). Elemental analysis was performed on a Carlo Erba 1106 (Italy) CHN analyzer. Melting points were measured on a Koffler block.

Commercially available $PdCl_2(PPh_3)_2$, 2-methyl-3-butyn-2-ol, diphenylacetylene, and benzil were used from the Aldrich company.

1,2-Bis(3,4-dimethoxyphenyl)ethyne (1) was prepared by method [3] in 80% yield with mp 156-157°C (mp 156-157°C [3]).

1,2-Bis(3,4-dimethoxyphenyl)ethane-1,2-dione (2). $KMnO_4$ (2.75 g, 17.0 mmol) was added to a solution of compound **1** (1.3 g, 4.4 mmol) in a mixture of acetone (35 ml), water (5 ml), and 80% acetic acid (2 ml). The product was refluxed for 8 h (TLC monitoring) and then cooled and filtered. The MnO_2 precipitate was washed on the filter with methylene chloride and the combined filtrate was washed with water and dried over Na_2SO_4. Solvent was evaporated *in vacuo* to give the product **2** (1.08 g, 74%) with mp 227-228°C (dioxane) (mp 219-220°C [4]).

2,3-Diphenylquinoxaline (4). A mixture of the benzil (**3**) (0.138 g, 0.7 mmol), *o*-phenylenediamine (0.076 g, 0.7 mmol), and CuI (50 mg) was refluxed in pyridine (10 ml) for 5.5 h. At the end of the reaction (TLC monitoring) the product was cooled, poured into benzene (50 ml), water (100 ml) added and extracted with benzene (5×20 ml). The combined organic extract was washed with an aqueous ammonia solution, dried over Na_2SO_4, filtered through an alumina layer (1×2.5 cm), and the solvent was evaporated *in vacuo* to give the product **4** (0.12 g, 60%) with mp 121-122°C (ethanol) (mp 124°C [5]).

3-(4-Nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (5). A mixture of 3,4,5-trimethoxybenzoyl chloride (2.3 g, 10 mmol), 1-ethynyl-4-nitrobenzene (1.47 g, 10 mmol), CuI (98 mg, 1 mmol), and Et_3N (3 ml) in toluene (20 ml) was stirred in an argon stream at 80°C for 8 h (TLC monitoring). The reaction product was cooled, filtered, and washed with aqueous ammonia solution to the formation of a colorless water fraction. The organic layer was dried over Na_2SO_4, filtered through an alumina layer (1×2.5 cm), and the solvent was evaporated *in vacuo* to give the product **5** (2.8 g, 82%) with mp 206-207ºC (ethyl acetate). IR spectrum, ν, cm^{-1}: 1132, 1162 and 1235 (O–CH_3), 1510 and 1590 (NO_2), 1646 (C=O), 2214 (C≡C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.25 (2H, d, *J* = 8.7, H-2,6); 7.8 (2H, d, *J* = 8.7, H-3,5); 7.4 (2H, s, H-2',6'); 3.93 (3H, s, OCH_3); 3.92 (6H, s, 2 OCH_3). Found, %: C 63.34; H 4.43; N 4.10. $C_{18}H_{15}NO_6$. Calculated, %: C 63.36; H 4.51; N 4.22.

5-(4-Nitrophenyl)-3-(3,4,5-trimethoxyphenyl)-1H-pyrazole (6). A mixture of ketone **5** (0.17 g, 0.5 mmol) and hydrazine hydrate (0.025 g, 0.5 mmol) in butyl alcohol (12 ml) was refluxed for 8 h (TLC monitoring). The reaction product was cooled and the product was filtered and recrystallized from ethanol to give compound **6** (0.1 g, 56%) with mp 227-228°C. IR spectrum, ν, cm^{-1}: 1104, 1237 and 1338 (O–CH_3), 1601 (NO_2), 3429 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.25 (2H, d, *J* = 8.8, H-2,6); 7.9 (2H, d, *J* = 8.8, H-3,5); 6.86 (1H, s, H-pyrazole); 6.82 (2H, s, H-2',6'); 3.89 (6H, s, 2OCH_3); 3.87 (3H, s, OCH_3). Found, %: *m/z* 355.1165 [M]. $C_{18}H_{17}N_3O_5$. Calculated: M 355.1163. Found, %: C 61.09; H 4.82; N 11.96. $C_{18}H_{17}N_3O_5$. Calculated, %: C 60.84; H 4.82; N 11.83.

2-Amino-4-(4-nitrophenyl)-6-(3,4,5-trimethoxyphenyl)pyrimidine (7). A mixture of ketone **5** (0.17 g, 0.5 mmol), 0.029 g (0.5 mmol) of a 1 M solution of guanidine prepared from guanidine hydrochloride (9.55 g, 100 mmol) and sodium (2.3 g, 100 mmol) in isopropanol (100 ml) was refluxed in *n*-butanol (12 ml) for 6 h (TLC monitoring). The reaction product was cooled, evaporated *in vacuo*, the residue was dissolved in ethyl acetate, the solution was filtered through an alumina layer (1×1.5 cm), and the filtrate was evaporated *in vacuo* to give compound **7** (0.1 g, 52%) with mp 229-231°C (dioxane). IR spectrum, ν, cm^{-1}: 1126, 1224 and 1347 (O–CH_3), 1615 (NO_2), 3372 and 3519 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.5 (2H, d, *J* = 8.9, H-2,6); 8.4 (2H, d, *J* = 8.88, H-3,5); 7.84 (1H, s, H pyrimidine); 7.54 (2H, s, H-2',6'); 6.9 (2H, s, NH_2); 3.87 (6H, s, 2OCH_3); 3.75 (3H, s, OCH_3). Found: *m/z* 382.1272 [M]. $C_{19}H_{18}N_4O_5$. Calculated: M 382.1271.

5-(4-Nitrophenyl)-3-(3,4,5-trimethoxyphenyl)isoxazole (8). A mixture of ketone **5** (0.17 g, 0.5 mmol), a solution of hydroxylamine (4 ml, 1 mmol) prepared from hydroxylamine hydrochloride (0.2 g, 3 mmol) and potassium hydroxide (0.2 g, 3 mmol) and potassium hydroxide (0.25 g, 4.5 mmol) in methanol (4 ml), in butyl alcohol (10 ml) was refluxed for 6 h (TLC monitoring). The cooled reaction mixture was evaporated *in vacuo*, the residue was dissolved in ethyl acetate, and the solution was filtered through an alumina layer. Evaporation of the filtrate *in vacuo* gave compound **8** (0.085 g, 48%) with mp 205-207°C (dioxane). IR spectrum, ν, cm^{-1}: 1125, 1237 and 1340 (O–CH_3), 1576 (NO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.4 (2H, d, *J* = 8.7, H-2,6); 8.2 (2H, d, *J* = 8.7, H-3,5); 7.9 (1H, s, H isoxazole), 7.2 (2H, s, H-2',6'); 3.9 (6H, s, 2OCH_3); 3.7 (3H, s, OCH_3). Found: *m/z* 356.1003 [M]. $C_{18}H_{16}N_2O_6$. Calculated: M 356.1001.

This work was carried out with financial support from the grants RUX0-008-NO-06/BP2M08, RFFI No. 07-03-0048a, and the Integrated grant of the Siberian Branch of the Russian Academy of Sciences No 54 and Chemistry Service Center of the Siberian Branch of the Russian Academy of Sciences.

REFERENCES

1. Le Wang, K. W. Woods, Qun Li, K. J. Barr, R. W. McCroskey, S. M. Hannick, L. Gherke, R. B. Credo, Yu-Hua Hui, K. Marsh, R. Warner, J. Y. Lee, N. Zielinski-Mozng, D. Frost, S. H. Rosenberg, and H. L. Sham, *J. Med. Chem.*, **45**, 1698 (2002).
2. K. Tanaka, Y. Konno, Y. Kuraishi, I. Kimura, T. Suzuki, and M. Kiniwa, *Bioorg. Med. Chem. Lett.*, **12**, 624 (2002).
3 A. P. Rudenko and A. V. Vasil'ev, *Zh. Org. Khim.*, **31**, 1512 (1995).
4. L. C. Raiford and W. F. Talbot, *J. Am. Chem. Soc.*, **54**, 1092 (1932).
5. G. Russel, E. Janzen, and T. Strom, *J. Am. Chem. Soc.*, **86**, 1814 (1964).