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Copper-Catalyzed Cyclization of Steroidal Acylaminoacetylenes: Syntheses of Novel 11*β*-Aryl-17,17-spiro[(4′*H*,5′-methylene)oxazol]-Substituted Steroids

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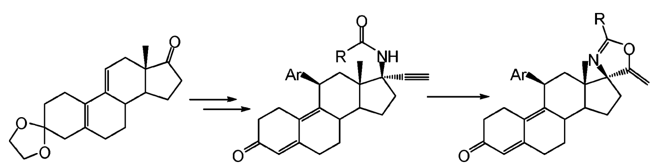
ABSTRACT



A variety of novel 11*β*-aryl-17,17-spiro[(4′*H*,5′-methylene)oxazol]-substituted steroids have been synthesized in moderate to good yields via copper-catalyzed cyclization of acylaminoacetylenes. The best result was obtained with a catalytic amount of CuI in 1:1 benzene–Et_3N at 90 °C for 30 min (Ar = 3,4-difluorophenyl; R = ethyl; 97% yield).

Progesterone, acting primarily via the progesterone receptor (PR), regulates the viability of cells of several different reproductive tissues, including the uterus, breast, cervix, and hypothalamic-pituitary unit.[1] It also has extra-reproductive activities such as effects on the brain, the immune system, the vascular endothelial system, and lipid metabolism. Given the wide array of effects, it is apparent that compounds which mimic some of the effects of progesterone (agonist), antagonize these effects (antagonist), or exhibit mixed effects (partial agonist or mixed agonist−antagonist) can be useful in the treatment of a variety of disease states and conditions.[2]

Since the discovery of the first competitive progesterone antagonist, mifepristone[3] (RU 486, **1**, Figure 1), hundreds of analogues have been synthesized to optimize the antiprogestational effect with regard to the steroid receptor selectivity.[4] It has been shown that substituents on the D-ring of the steroid can have a marked influence on the biological profile of these compounds. The earliest antiprogestins were substituted with a 17*β*-hydroxyl group and various 17α-

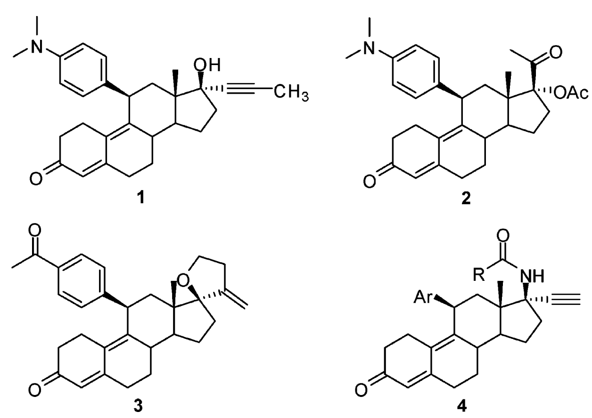


Figure 1. Antiprogestins.

[†] Dr. C. Edgar Cook is deceased.
(1) Spitz, I. M. *Steroids* **2003**, *68*, 981.
(2) Chabbert-Buffet, N.; Meduri, G.; Bouchard, P.; Spitz, I. M. *Hum. Reprod. Update* **2005**, *11*, 293.
(3) Teutsch, G.; Costerousse, G.; Philibert, D.; Deraedt, R. U.S. Patent 4 386 085, 1983.

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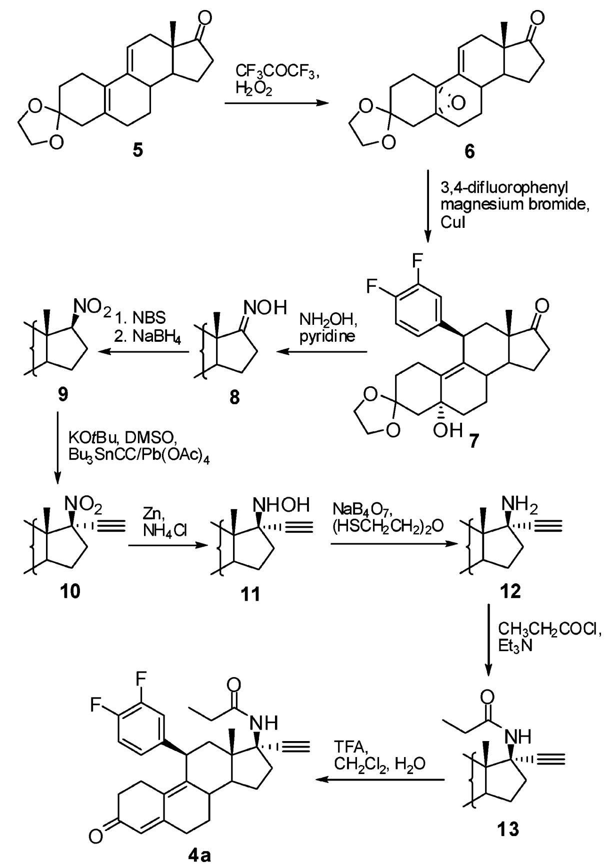
substituents.[5] Replacement of these substituents with the progesterone side chain (17β-acetyl) together with a 17α-acetoxy substituent led to RTI-3021-012 (also known as CBD 2914) (**2**), which is approximately 3 times as potent as mifepristone.[6] In addition, exchange of the 17-side chain with 17,17-spirocyclic moieties characterized by a sulfur,[7] nitrogen,[8] or oxygen[9] enhanced antiprogestational effects, in some cases, with considerably reduced antiglucocorticoid activities. In fact, one of the most active compounds in this series, ORG 33628 (**3**), has been claimed to be 16 times as active as RU 486 in the pregnancy interruption test in rats and about 6 times less active as an antiglucocorticoid.[10]

Some time ago, we found that various 17β-nitro[8] and amino substituents[11] (e.g., **4a**; Ar = 3,4-difluorophenyl, R = ethyl) could also generate antiprogestational effects. To find highly potent antiprogestins with considerably reduced endocrine side effects, we have continued the investigation of the C(17) modification of **4**. Recently, a variety of oxazolines,[12] benzoxazines,[13] quinazolin-2-ones, quinazolin-3-ones, and indoles[14] have been successfully synthesized by the palladium-catalyzed or the copper-catalyzed[14b] cyclization of alkynes having an acylamino group in close proximity to the carbon−carbon triple bond. We now report here the cyclization of ethynes **4** to generate novel spiro-oxazole moieties at the C(17) position.

The key intermediate **4a** for our study was prepared in 24% yield from commercially available 3,3-[1,2-ethanediylbis(oxy)]estra-5(10),9(11)-dien-17-one (**5**) following the reported procedure (Scheme 1).[8,11] The regioselective 5,10-epoxidation of **5** was achieved by using hexafluoroacetone hydroperoxide generated in situ from hexafluoroacetone trihydrate and hydrogen peroxide to give **6** in 53% yield. The CuI-catalyzed addition of 3,4-difluorophenyl magnesium bromide gave the corresponding Grignard adduct **7** in 92% yield.[15] Oxime formation with hydroxylamine hydrochloride in pyridine provided **8** quantitatively. Teatment of **8** with

Scheme 1

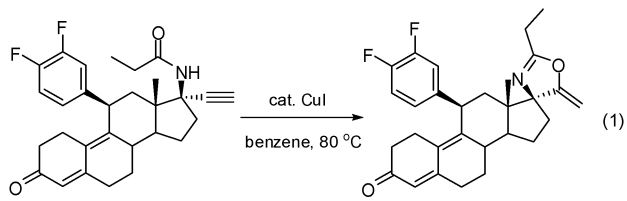


N-bromosuccinimide (NBS)[16] gave the 17-bromo-17-nitro compound, which was readily reduced by $NaBH_4$ to the 17β-nitro compound **9** as confirmed by ^{1}H NMR analysis. The C(17)-H presented a triplet signal at δ 4.34 with a coupling constant of 6.1 Hz, a pattern that is consistent with the usual finding for an α C(17) hydrogen atom.[17] The 17α-ethynyl substituent was then introduced into the nitro compound **9** by treatment of the anion of **9** in dimethyl sulfoxide (DMSO) with ethynyllead(IV) triacetate.[18] 17α-Ethynyl-17β-nitro compound **10** was isolated as a single diastereoisomer in 81% yield. The stereochemistry at C(17) in **10** was assigned based on comparison of its NMR spectra with that of known compounds.[8,19] Reduction of **10** with zinc dust at 0 °C gave hydroxylamine **11**, which upon treatment with sodium tetraborate, ammonium iron(II) sulfate, and 2-mercaptoethyl ether[20] afforded an 82% yield of amine **12**. Finally, acylation with propionyl chloride followed by deketalization and dehydration with trifluoroacetic acid (TFA) provided 11β-

(4) Teutsch, G.; Philibert, D. *Hum. Reprod.* **1994**, *9* (1), 12.
(5) For example: (a) Wiechert, R.; Neef, G. *J. Steroid Biochem.* **1987**, *27*, 851. (b) Wehle, H.; Moll, J.; Cato, A. C. B. *Steroids* **1995**, *60*, 368. (c) Fuhrmann, U.; Hess-Stumpp, H.; Cleve, A.; Neef, G.; Schwede, W.; Hoffmann, J.; Fritzemeier, K. H.; Chwalisz, K. *J. Med. Chem.* **2000**, *43*, 5010.
(6) (a) Cook, C. E.; Wani, M. C.; Lee, Y.-W.; Fail, P. A.; Petrow, V. *Life Sci.* **1993**, *52*, 155. (b) Cook, C. E.; Lee, Y.-W.; Wani, M. C.; Fail, P. A.; Petrow, V. *Hum. Reprod.* **1994**, *9* (1), 32.
(7) Cook, C. E.; Shetty, R. S.; Kepler, J. A.; Lee, D. Y.-W. U.S. Patent 6 043 235, 2000.
(8) Cook, C. E.; Kepler, J. A.; Shetty, R. S.; Lee, D. Y.-W. U.S. Patent 6 015 805, 2000.
(9) (a) Philibert, D.; Hardy, M.; Gaillard-Moguilewsky, M.; Nique, F.; Tournemine, C.; Nédélec, L. *J. Steroid Biochem.* **1989**, *34*, 413. (b) Nioue, F.; Nedelec, L.; Philibert, D.; Moguilewsky, M. U.S. Patent 4 900 725, 1990.
(10) (a) Kloosterboer, H. J.; Deckers, G. H.; de Gooyer, M. E.; Dijkema, R.; Orlemans, E. O.; Schoonen, W. G. *Ann. N.Y. Acad. Sci.* **1995**, *761*, 192. (b) Kloosterboer, H. J.; Deckers, G. H.; Schoonen, W. G.; Hanssen, R. G.; Rose, U. M.; Verbost, P. M.; Hsiu, J. G.; Williams, R. F.; Hodgen, G. D. *Steroids* **2000**, *65*, 733.
(11) Cook, C. E.; Kepler, J. A.; Bartley, G. S. U.S. Patent 6 262 042, 2001.
(12) Bacchi, A.; Costa, M.; Gabriele, B.; Pelizze, G.; Salerno, G. *J. Org. Chem.* **2002**, *67*, 4450.
(13) Costa, M.; Cà, N. D.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2003**, *69*, 2469.
(14) (a) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843.
(15) Teutsch, G.; Klich, M.; Bouchoux, F.; Cerede, E.; Philibert, D. *Steroids* **1994**, *59*, 22.
(16) Patchett, A. A.; Hoffman, F.; Giarrusso, F. F.; Schwam, H.; Arth, G. E. *J. Org. Chem.* **1962**, *27*, 3822.
(17) Krohn, K.; Küpke, J. *Eur. J. Org. Chem.* **1998**, 679.
(18) Moloney, M. G.; Pinhey, J. T.; Roche, E. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 333.
(19) The stereochemistry of **10** was further confirmed based on the NMR studies of the cyclization product **14a**.
(20) Nambu, Y.; Kijima, M.; Endo, T.; Okawara, M. *J. Org. Chem.* **1982**, *47*, 3066.

(3,4-difluorophenyl)-17α-ethynyl-17β-[(1-oxopropyl)amino]-estra-4,9-dien-3-one (**4a**) in 87% yield.

An attempt at Sonogashira-type acylation[21] of the ethynyl group of **4a** with *N*,*N*-dimethylcarbamoyl chloride under standard conditions [$Pd(PPh_3)_2Cl_2/PPh_3$/CuI/benzene/Et_3N/90 °C[22]] led to none of the coupling product. Instead, the major product isolated in 68% yield was identified as **14a** (see below). To determine which of the reagents was essential for this reaction to occur, the cyclization of **4a** was first carried out with 10 mol % of CuI in refluxing benzene for 24 h (eq 1). The cyclization product **14a** was isolated in 30%



yield and a 65% yield of **4a** was recovered (Table 1). The 6-membered regioisomer oxazine was not detected by ^{1}H NMR analysis of the crude product mixture. The structure of **14a** was confirmed by NMR studies (Supporting Information), particularly with the aid of 2D proton−proton (gCOSY) and proton−carbon (gHMBC and gHSQC) correlation spectroscopy techniques. The two terminal vinylic protons were clearly evident at δ 4.80 and 4.20 with a coupling constant of 2.5 Hz.

Table 1. Optimization of Cyclization of Acylaminoacetylene **4a**

catalyst[a]	solvent	temp (°C)	time (h)[c]	% isolated yield
CuI	benzene	80	24	30
CuI	DMF	90	2	trace[d]
CuI	DMSO	90	2	trace[d]
CuI	benzene−Et_3N	90	0.5	97
CuI	benzene−Et_3N	40	24	46
$Pd(OAc)_2$	benzene−Et_3N	90	1	54
$AgNO_3$[b]	benzene−Et_3N	90	3	84
$HgCl_2$	benzene−Et_3N	90	3	9

[a] 10 mol % of catalyst was used. [b] 1.1 equiv of $AgNO_3$ was used. [c] The progress of reaction was monitored by TLC, and the reaction worked up after approximately 100% conversion or after 24 h of reaction time. [d] Determined by ^{1}H NMR spectroscopy.

The stereochemistry of **14a** was construed from analysis of the molecular model, energy minimized with the MMFF94 force field in Spartan’04 (Wavefunction, Inc., Irvine, CA) overlaid with key correlations observed in the two-dimensional ROESY NMR spectrum (Figure 2). Strong correlations were observed between vinylic H_a and C(14)-H, and between vinylic H_a and α C(16)-H, indicating that these respective pairs of protons were proximal. In addition, no correlations between vinylic protons and the C(18) methyl group were observed. The calculated interatomic distances of approximately 2.2 Å between vinylic H_a and C(14)-H, and 2.6 Å between vinylic H_a and α C(16)-H are consistent with the observation of strong ROESY correlations. On the basis of the comparison with the known stereochemistry at carbons C(8), C(13), and C(14), the stereochemistry at C(17) of **14a** was assigned as shown in Figure 2.

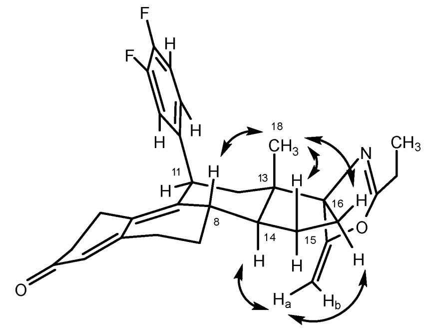


Figure 2. Key ROESY correlations of **14a**.

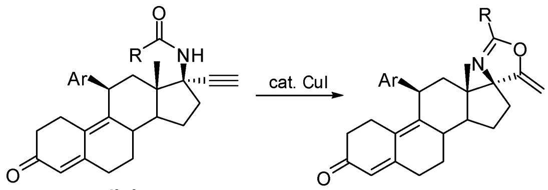
The CuI-catalyzed cyclization of **4a** was also tried by using dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) as the solvent, but this resulted in decomposition of **4a** (Table 1). Only a small amount of desired product **14a** was detected in the reaction mixture. After further optimization, it was found that treatment of **4a** in a 1:1 mixture of benzene and Et_3N at 90 °C in the presence of 10 mol % of CuI led to rapid cyclization (30 min) to produce **14a** in 97% yield. Lowering the temperature to 40 °C gave **14a** in only 46% yield even after 24 h of reaction time. This cyclization could also be catalyzed by other transition metal salts such as $Pd(OAc)_2$ and $AgNO_3$ with acceptable yields. However, when $HgCl_2$ was used as a catalyst, only a 9% yield of **14a** was realized. The optimal cyclization conditions thus far developed employ 1 equiv of the substrate **4a** (0.2 mmol) and 10 mol % of CuI in 1:1 benzene−Et_3N (4 mL) at 90 °C.

By employing this protocol, a number of steroidal acylaminoacetylenes **4b**−**j**[23] were cyclized to give the corresponding spiro-oxazoles in moderate to good yields (Table 2). Generally, the cyclization of acetyl and propionamides was completed within 1 h to give the corresponding spiro-oxazoles in 83−93% yields. In the case of formyl and trifluoroacetylamides, the cyclization products were isolated in moderate yields (40−60%) with incomplete conversion of the starting material. Use of longer reaction times to consume all the starting material led to decomposition and lower yield of the cyclization product. We believe that a reasonable mechanism for this copper-catalyzed cyclization of terminal acetylenes involves CuI coordinating to the carbon−carbon triple bond to form a copper−acetylene π complex,[24] followed by Et_3N assisted intramolecular nucleo-

(21) Tohda, Y.; Sonogashira, K.; Haghiara, N. *Synthesis* **1977**, 777.
(22) The reaction temperature was given as the temperature of the heating bath.

(23) The steroidal acylaminoacetylenes **4b**−**j** were prepared following the similar synthetic route in Scheme 1.

Table 2. Syntheses of 11β-Aryl-17,17-spiro[(4′*H*,5′-methylene)oxazol]-Substituted Steroids[a]



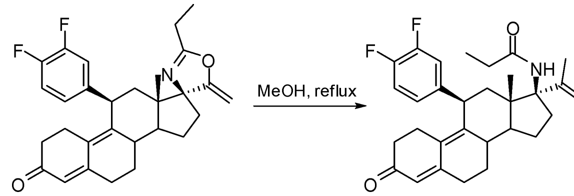
4b-j 14b-j

product	Ar	R	% yield[b]
14b	3,4-difluorophenyl	CH_3	91
14c	3,4-difluorophenyl	CF_3	45
14d	4-(*N*,*N*-dimethylamino)phenyl	CH_2CH_3	93
14e	4-(*N*,*N*-dimethylamino)phenyl	CH_3	91
14f	4-(*N*,*N*-dimethylamino)phenyl	CF_3	63
14g	4-(*N*,*N*-dimethylamino)phenyl	H	38
14h	4-acetylphenyl	CH_2CH_3	85
14i	4-acetylphenyl	CH_3	83
14j	4-acetylphenyl	H	40

[a] All reactions were carried out under the optimal conditions reported in the text. [b] Isolated yield.

philic attack of the oxygen of the amide moiety on the activated carbon−carbon triple bond.

The prepared steroidal spiro-oxazoles **14a−j** are stable at room temperature. However, they are readily hydrolyzed upon treatment with harsher conditions (e.g., refluxed in MeOH). When **14a** was heated in refluxing MeOH for 16 h, the hydrolysis product 17α-acetyl-17β-propionylamino-substituted steroid **15** was obtained in 96% yield (eq 2).



14a 15 (2)

In conclusion, we have established an efficient copper-catalyzed cyclization of steroidal acylaminoacetylenes to give the corresponding 11β-aryl-17,17-spiro[(4′*H*,5′-methylene)-oxazol]-substituted steroids in moderate to good yields. The corresponding 17α-acetyl-17β-acylamino steroids were then obtained by hydrolysis. The hormonal properties of these novel steroids will be reported separately.

Acknowledgment. This work was supported by the R. W. Johnson Pharmaceutical Research Institute.

Supporting Information Available: Experimental procedures and characterization data for the reported reactions, NMR assignments of **14a**, and NMR spectra of **4a−j**, **14a−j**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070447D

(24) Macomber, D. W.; Rausch, M. D. *J. Am. Chem. Soc*. **1983**, *105*, 5325.