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AN IMPROVED ALTERNATIVE NORGESTREL PREPARATION

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ABSTRACT. Ethynyl cerium chloride, prepared *in situ* from ethynyl magnesium bromide or lithium acetylide and anhydrous cerium chloride efficiently added to 13-ethyl-3-methoxy-gona-3,5-diene-17-one **2.** Aqueous HCl hydrolysis of intermediate enol ether **3** gave high yields of norgestrel **4**.

Norgestrel[2,3] (17α-ethynyl-18-methyl-19-nortestosterone) **4** is an excellent progestational and ovulation inhibiting steroid. A review on **4** the total syntheses of this steroid has been published recently.[4] Here we would like to report an alternative, high yielding procedure to introduce the ethynyl moiety in the 17-position of precursor **1**, a reaction which is of particular relevance to the final steps in the synthesis of Norgestrel **4**.

Direct ethynylation on 13-ethyl-3,17-dione **1** has been reported,[5] although no experimental details were given. In fact we have found that various ethynylating

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reagents (LiC≡CH/EDA, HC≡CMgBr, HC≡CNa, LiC≡CH) added to both 3- and 17-carbonyls of **1** and in the best cases only minor quantities of **4** were detected. 13-Ethyl-3-methoxy-gona-3,5-diene-17-one **2** proved to be a better substrate. Compound **2** was obtained in 82% yield through an exchange ketal reaction with 2,2-dimethoxypropane in DMF as a solvent and PTSA as catalyst, following a related literature procedure.[6]

Ethynylation of **2** with ethynyl magnesium bromide gave a better reaction profile and improved yield. However the reaction was incomplete even after prolonged (24 h) heating (60 °C). Lithium acetylide showed a similar behaviour. The low reactivity exhibited by 13-ethyl-17-keto steroids to acetylenic nucleophiles has been explained in terms of an extra steric hindrance provided by the bulky ethyl group.[7] One can further speculate whether the 17-carbonyl could be enolized thus preventing access to the nucleophile.

Reactions of highly enolized carbonyl compunds with Grignard or lithium reagents have been shown to proceed well if assisted by cerium chloride.[8] Accordingly ethynyl cerium chloride[9] formed *in situ* from ethynyl magnesium bromide and cerium chloride was treated with enol ether **2** and the reaction showed complete consumption of starting material within an hour. After acid hydrolysis of the intermediate enol ether **3**, Norgestrel **4** was isolated in 91% yield. Similarly, the combination ethynyl lithium and cerium chloride gave Norgestrel in 80% isolated yield.

It thus seems that the ethynyl cerium reagent indeed has an enhanced nucleophilicity, which facilitates addition not only to enolized carbonyls but to hindered ones as well.

Typical procedure. Under a nitrogen atmosphere, dry THF (10 ml) was added to anhydrous cerium chloride[8] (2.5 g, 6.7 mmol) and the resulting suspension was stirred for 2 h at room temperature. EGD enol ether **2** (0.43 g, 1.43 mmol) was dissolven in THF (10 ml) and the sdolution added to the $CeCl_3$-THF suspension, stirring was continued for an additional hour. Ethynyl magnesium bromide (0.5 M THF solution) (0.4 g, 3.1 mmol) was then gradually added at room temperature. Reaction progress was tlc monitored. After one hour satd. aqueous NH_4Cl was added and the whole stirred for 0.5 h at room temperature. THF was separated from the aqueous phase and concentrated under vacuum. Aq. (10%) acetic acide (15 ml) was added to the water phase and further extracted with CH_2Cl_2 (2 x 25 ml). Organic extracts were combined and washed with aq. $NaHCO_3$ (1 x 100 ml) and water (1 x 100 ml), dried (anh. Na_2SO_4) and concentrated under reduced pressure. Methanol (20 ml) was then added and the formed suspension warmed to allow stirring. The suspension was cooled to 10 °C., 3N HCl (60 ml) added and a precipitate immediately formed. Stirring was continued for 0.5 h at 0 °C. The solid was filtered and succesively washed with cold water (l x 10 ml), cold water/EtOH (1/1) (l x 10 ml) and hexane (l x 10 ml) Norgestrel was isolated as a pale yellog solid (0.41 g, 92 %). IR and HNMR spectra conformed norgestrel structure. No depression in a mixed m.p. (204-206 ^{0}C, lit.[10] m.p. 205-207 °C) with an authentic sample of norgestrel was observed.

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