HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 779 - 783, Received, 25th September, 2002

A FACILE ACCESS TO 2-ETHYNYL-1,4-DIHYDROPYRIDINES *VIA* HANTZSCH THREE-COMPONENT REACTION

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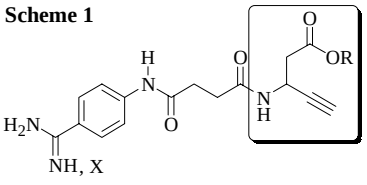
Abstract – A new synthesis of 2-ethynyl-1,4-dihydropyridine derivatives in two steps from alkyl 3-oxo-5-trimethylsilyl-4-pentynoates *via* the Hantzsch three-component reaction followed by an alkaline hydrolysis is described.

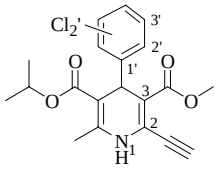
Introduction

2-Ethynylamino esters have numerous applications in biology and synthetic chemistry. SC-54701A (**1**),[1] its prodrug ester (**2**)[1] and 2-ethynyl-1,4-dihydropyridine (DHP) derivative (**3**)[2] have significant pharmacological properties such as platelet aggregation inhibitors (fibrinogen receptor antagonists)[1] and increasing coronary blood flow[2,3] (Scheme 1).

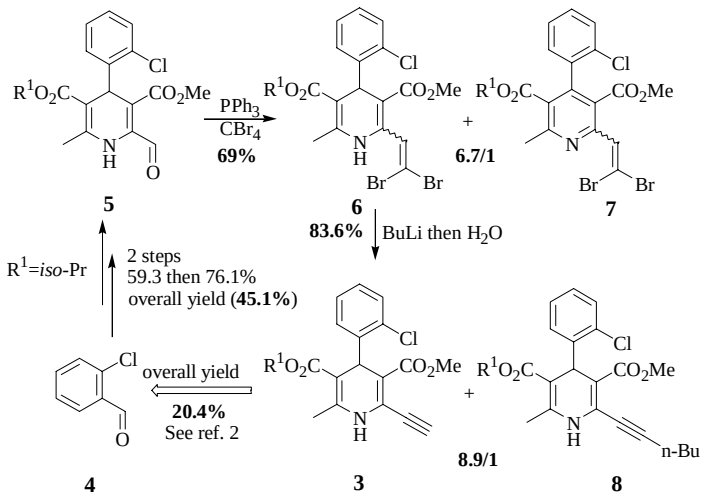
Scheme 1



(**1**) R=H (**SC-54701**), X=HCl
(**2**) R=Et (**Prodrug ester**), no X



(**3**) **Coronary Blood Flow**
Ar = 2-ClPh-



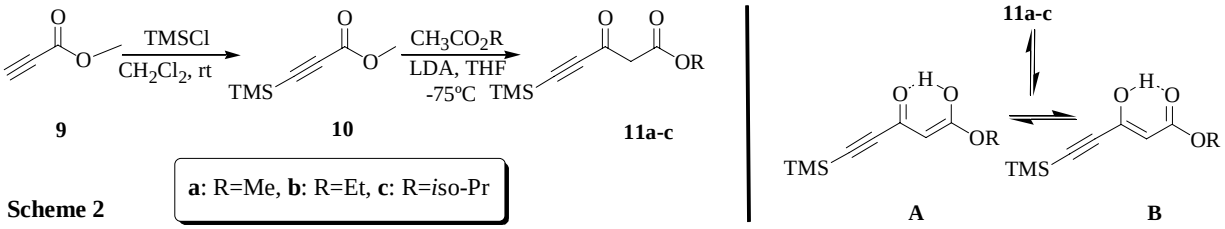
5 **6** **7** **4** **3** **8**

The only known 2-ethynyl-1,4-DHP (**3**) was reported by Satoh *et al.*[2] derived from 2-formyl-1,4-DHP (**5**) according to the method developed by Corey *et al.*,[4] in which **3** was isolated in an overall yield of 20.4%[5] and was accompanied by the formation of **8** in small amount (Scheme 1).[6]

In the connection with our research program directed towards the synthesis and the use of the 1,4-DHP polyheterocycles,[7] we report herein a three-component Hantzsch type 1,4-DHP synthesis.[8]

Results and Discussion

Initially, a series of 3-oxo-5-trimethylsilyl-4-pentynoates (**11a-c**) with different ester group (R=Me, Et, *iso*-Pr) were prepared from **9** in a two steps according to the reported procedure.[9] The trimethylsilylation of methyl propiolate (**9**) by TMSCl in CH_2Cl_2 at room temperature gave methyl 3-trimethylsilylpropiolate (**10**) in 95% yield (Scheme 2). Reaction of **10**[9] with methyl lithioacetates,[10] which prepared *in situ* from methyl acetate and LDA as a base at –75°C, gave β-keto esters (**11a-c**).[10,11]

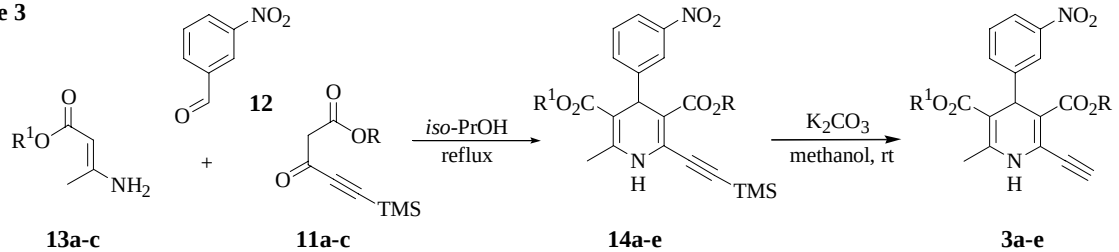


Scheme 2

Interestingly, the ^{1}H NMR spectra of compounds (**11a-c**) recorded in $CDCl_3$ show, in addition to the singlet signal of the methylene protons at δ=3.44 to 3.60 ppm in the β-keto ester form, a low field singlet 1H assigned to the vinylic proton =CH at δ=5.22 to 5.39 ppm for the enol ester form (**A**) or (**B**) which is best described by the tautomeric structures (**11**)↔(**A**)↔(**B**) (Scheme 2). The ratios of these forms was 1/1 for β-keto esters (**11a,b**) (R=Me, Et) and 2/1 for β-keto ester (**11c**) (R=*iso*-Pr) in favour of the keto ester form.[12] This fact, was also confirmed by the presence of the exchangeable signal of the chelate proton (δ=1.63 to 2.15 ppm) when D_2O was added to $CDCl_3$ solution of the silylated compounds (**11a-c**).

In the first set of our Hantzsch type three-component reaction experiments, 3-nitrobenzaldehyde (**12**)[13] (Scheme 3) was subjected to reaction with 1.05 equiv. of **11a** and 1.1 equiv. of **13a** in *iso*-propanol by simply heating at reflux for 3 to 5 h. The product (**14a**) was isolated by chromatography on silica gel column (hexane/ethyl acetate (10/1)) followed by recrystallisation from a mixture of ligroin/ethyl acetate (3/4) in 20% yield (Table 1, Run 1).

Scheme 3



The desilylation from **14a** proceeded smoothly with potassium carbonate in methanol (Scheme 3) at room temperature to give 2-ethynyl-1,4-DHP (**3a**) after recrystallisation from a mixture of ligroin/ethyl acetate (3/4) in 89% yield (Table 1, Run 1).[14]

Table 1: 2-(2-Trimethylsilanyl)ethynyl-1,4-DHPs (**14a-e**) and corresponding 2-ethynyl-1,4-DHPs (**3a-e)**.

Run	R group	R_1 group	Product[a]	Yield (%)[b]	mp (°C) [c]	Product	Yield (%)[b]	mp (°C) [c]	Overall yield (%)
1	Me	Me	**14a**	20	187-189	**3a**	89	183-185	17.8
2	Et	Me	**14b**	35	180-182	**3b**	95	138-140	33.5
3	*i*.Pr	Me	**14c**	32	160-161	**3c**	80	152-154	25.5
4	*i*.Pr	Et	**14d**	30	150-152	**3d**	87	163-165	26.1
5	*i*.Pr	*i*.Pr	**14e**	25	131-133	**3e**	75	126-128	18.7

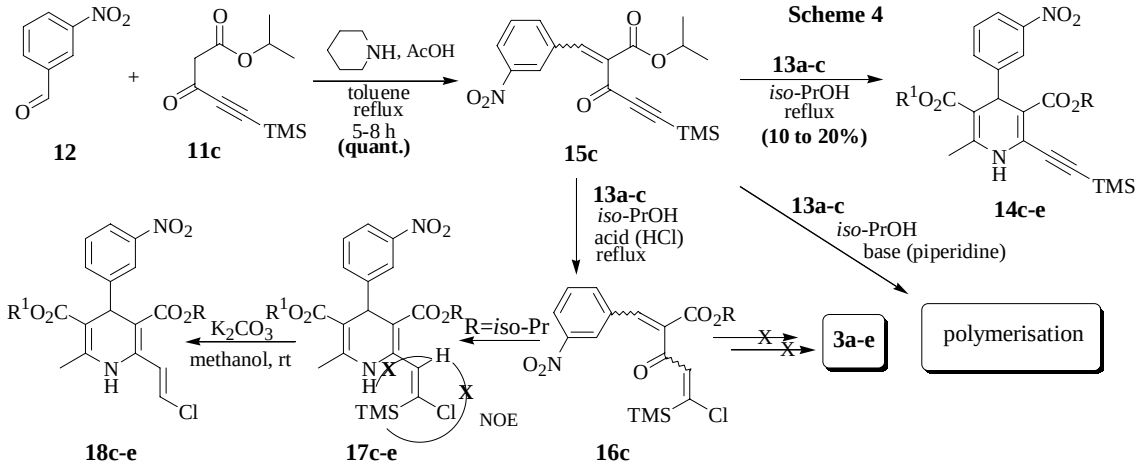
[a] The reactions were performed on 2-4 mmol using 1.05 equiv. of silylated reagents (**11a-c**) and 1.1 equiv. of enamino ester derivatives (**13a-c**) at reflux.
[b] The indicated yields were obtained after purification by chromatography on silica gel column and recrystallisation.
[c] In general, the mp measurements were accompanied with the decomposition of the products.

In a similar manner as above, the reaction of 3-nitrobenzaldehyde (**12**), **13** and **11** afforded 2-(2-trimethylsilanyl)ethynyl-1,4-DHPs (**14b-e**) in a range of 25-35% yields (see Table 1). The labile trimethylsilyl group was removed under basic conditions in the same manner as above to form the 2-ethynyl-1,4-DHPs (**3b-e**). These products were isolated in a range of 75-95% yields after recrystallisation (Table 1).

Under the light of these results, we can therefore assume that there was no discernible preference for the nature and the range of the substituents R and R_1 groups since the DHP skeletons (**3a-e**) were observed in comparable yields. These results also indicated clearly that the keto/enol ratio in the β-keto ester (**11**), did not constitutes an important factor during the Hantzsch protocol but the lowest of the yield of this cyclocondensation is due to the fragility of the silylated product (**15c**) itself as the Knoevenagel intermediate, obtained by condensation of the formyl (**12)** and the methylene (**13**) reagents.

To test this hypothesis, and in order to increase the overall yield of the 2-ethynyl-1,4-DHP compounds (**3a-e**), we first investigated the Knoevenagel condensation of the aldehyde (**12)** and silylated β-keto ester (**11c**), with a catalytic amount of piperidinium acetate under azeotropic conditions to give quantitatively the benzylidene derivative (**15**) (Scheme 4).[7]

Scheme 4



Heating **15c** and amino esters (**13a-c**) in anhydrous *iso*-propanol gave (**14c-e**) but in mediocre yields (10 to 20%). In the same manner, use of base (piperidine, pyrrolidine, etc...) as a catalyst, either at reflux or at room temperature for prolonged time, proved unsuccessful and the reaction was accompanied with total destruction of the starting benzylidene substrate (**15c**). Interestingly, gaseous hydrogen chloride treatment of **15c** gave cleanly rise to the 2-(2-chloro-2-trimethylsilanyl)vinyl-1,4-DHPs (**17c-e**) (54 to 60%). This result can be explained by invoking a HCl addition onto the triple bond (Scheme 4), and the exclusive and more reactive intermediate (**16c**) obtained, after an ultimate Hantzsch cyclisation step, leads to formation of 1,4-DHP nucleus bearing the vinyl group at the 2-position as a single isomer.[15] Furthermore, taking into account that **17c-e** bear a trimethylsilyl group and an halide atom which could potentially cleaved, tentative of their displacement were partially achieved when K_2CO_3 in methanol at room temperature was used. The sole products (**18c-e**) were isolated in good yields (65 to 77%) and the olefin geometry was established as *trans* identical to that of their congeners (**17c-e**). Finally, further study in reaction conditions to form ethynyl products (**3**) from these substrates (**17c-e**) is under investigations.

Conclusion

We have demonstrated in this paper, that Hantzsch type three-component reaction constitutes a facile and effective process to 2-ethynyl-1,4-DHPs (**3a-e**). The reaction proceeded without activation in two steps (overall yield of 17.8-33.5%) but in the presence of an additional acid as a catalyst, the reaction take an other way to furnish 2-(2-chlorovinyl)-1,4-DHPs (**18c-e**).

REFERENCES AND NOTES

1. J. Cossy, A. Schmitt, C. Cinquin, D. Buisson, and D. Belotti, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1699.
2. Y. Satoh, M. Ichihashi, and K. Okumura, *Chem. Pharm. Bull.*, 1991, **39**, 3189.
3. The activity of this product is due to the ethynyl group at C_2 which resembles a nitrile one (see the calcium modulators Nilvadipine family) in terms of electronic structure and also in sterical bulkiness. In contrary the 2-vinyl-, 2-acetyl- and 2-formyl-1,4-DHP derivatives were all inactive.
4. E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769.
5. The 2-ethynyl-1,4-DHP product (**3**) (Ar=*o*-Cl-C_6H_4) was obtained in 4 or 5 steps from 2-chlorobenz-aldehyde (**4**) according to the Hantzsch type cyclocondensation followed by the Corey's method.
6. The presence of $–NO_2$ group instead of –Cl one on the aromatic nucleus at C_4-position of the DHP ring, proved the Corey's approach to homologous of **3** more difficult, associated with lower yield, not reproducible and finally unsuccessful.
7. (a) M. Chudík, Š. Marchalín, and K. Harvilová, *Collect. Czech. Chem. Commun.*, 1998, **63**, 826. (b) M. Chudík, Š. Marchalín, D.-P. Pham-Huu, O. Humpa, and Z. Friedl, *Monatsh. Chem*., 1999, **130**, 1241. (c) M. Chudík, Š. Marchalín, P. Knesl, A. Daïch, and B. Decroix, *J. Heterocycl. Chem.*, 2000, **37**, 1549. (d) M. Chudík, Š. Marchalín, P. Knesl, A. Daïch, and B. Decroix, *Res. Adv. Synth. Org. Chem.*, 2000, **1**, 1. (e) Š. Marchalín, K. Cvopová, D.-P. Pham-Huu, M. Chudík, J. Kožíšek, I. Svoboda, and A. Daïch, *Tetrahedron Lett.*, 2001, **42**, 5663. (f) Š. Marchalín, M. Chudík, K. Cvopová, J. Kožíšek, J. Leško, and A. Daïch, *Tetrahedron*, 2002, **58**, 5747.
8. (a) A. Hantzsch, *Justus Liebigs Ann. Chem.*, 1882, **215**, 1. (b) A. Hantzsch, *Ber.*, 1890, **23**, 1474.
9. For the Claisen condensation protocol, see the following reference: H. H. Wasserman, R. Frechette, T. Oida, and J. H. Van Duzer, *J. Org. Chem.*, 1989, **54**, 6012.

10. To our surprise, this compound (**11a**) was only briefly mentioned in the literature and was obtained by condensation of methyl lithioacetate with ethyl propiolate instead methyl propiolate used in our case. For this end see the following article: M. H. Ansari, T. Kusumoto, and T. Hiyama, *Tetrahedron Lett.*, 1993, **34**, 8271.
11. (a) Compound (**11b)** (R = Et) was prepared also from ethyl propiolate in an excellent yield of 95% (bp=83-85°C/2 mm Hg). For this end, see ref. 1. (b) Selected data for the unknown *iso*-propyl 3-oxo-5-(trimethylsilanyl)pent-4-ynoate (**11c**): Yield=70%; bp 70-75°C/0.05 torr; IR: 2982 (C-H), 2155 (C≡C), 1718 (C_1=O), 1079, 1611 (C_3=O), 1252 (COC); ^{1}H-NMR ($CDCl_3$): δ 5.32 (s, 1H, C<u>H</u>), 5.06 and 5.05 (2xm, 1H, O-C<u>H</u>), 3.52 (s, 2H, C<u>H</u>$_2$), 2.15 (s, 1H, O<u>H</u>), 1.26 and 1.24 (2xd, *J*=6.5 Hz, 6H, CH(C<u>H</u>$_3$)$_2$), 0.22 and 0.21 (2xs, 9H, Si(C<u>H</u>$_3$)$_3$); ^{13}C-NMR ($CDCl_3$): δ (oxo) 178.3 (C=O), 165.2 (<u>C</u>O$_2$CH), 101.0 (≡<u>C</u>-C=O), 98.0 (≡<u>C</u>-Si), 69.0 (O-<u>C</u>H), 51.3 (CH_2), 21.6 (CH(<u>C</u>H$_3$)$_2$), -1.1 ((<u>C</u>H$_3$)$_3$-Si); (enol) 171.6 (<u>C</u>O$_2$CH), 154.3 (<u>C</u>-OH), 99.9 (≡<u>C</u>-C-OH), 98.0 (≡<u>C</u>-Si), 97.9 (<u>C</u>H), 68.1 (O-CH(<u>C</u>H$_3$)$_2$), -0.8 ((<u>C</u>H$_3$)$_3$Si).
12. No indication has been done in the literature concerning such keto-enol tautomerism in these γ-ethynyl-β-keto ester products.
13. The use of 3-nitrobenzaldehyde instead 2-chlorobenzaldehyde was chosen to test the feasibility of our approach in comparison to the Corey's one which was unsuccessfully with this formyl substrate.
14. General procedure for the three-component Hantzsch reaction leading to silylated products (**14**) and their desilylation into 2-ethynyl-1,4-DHPs (**3**): A mixture of 3-nitrobenzaldehyde (**12**) (0.6 g, 4 mmol), β-keto ester (**11**) (4.4 mmol) and enamino ester (**13)** (4.4 mmol) in 10 mL of dry *iso*-propanol was refluxed for 3 to 5 h. The solvent was evaporated carefully under reduced pressure to give an oil alkyne (**14**) which was purified by column chromatography on silica gel (hexane/ethyl acetate (10/1)) followed by recrystallisation from a mixture of ligroin/ethyl acetate (3/4) (20 to 35% yield).
    Selected data for dimethyl 6-methyl-4-(3-nitrophenyl)-2-(2-trimethylmethylsilanyl)ethynyl-1,4-dihydropyridine-3,5-dicarboxylate (**14a**): yield=20%; mp 187-189°C; IR: 3338 (NH), 3086 (=CH), 2967 (CH), 3248, 3222 (C≡C), 1701, 1689 (CO), 1649 (C=C), 1528 (NO_2), 1210 (COC); MS (EI, 70 ev) *m/z*: 428 (12, M^+); ^{1}H-NMR ($CDCl_3$): δ 8.12 (s, 1H, <u>H</u>$_8$-Ar), 8.02 (d, *J*=8.1 Hz, 1H, <u>H</u>$_{10}$-Ar), 7.66 (d, *J*=7.7 Hz, 1H, <u>H</u>$_{12}$-Ar), 7.40 (t, *J*=7.9 Hz, 1H, <u>H</u>$_{11}$-Ar), 6.22 (s, 1H, N<u>H</u>) 5.18 (s, 1H, <u>H</u>$_4$), 3.70 (s, 3H, OC<u>H</u>$_3$), 3.65 (s, 3H, OC<u>H</u>$_3$), 2.41 (s, 3H, C<u>H</u>$_3$), 0.25 (s, 9H, Si(C<u>H</u>$_3$)$_3$); ^{13}C-NMR ($CDCl_3$): δ 167.1 (C=O), 165.9 (C=O), 148.4 (C), 148.3 (C), 145.7 (C), 134.3 (CH), 128.9 (CH), 127.4 (C), 122.8 (C), 121.7 (CH), 111.0 (C), 104.3 (C), 101.5 (C), 97.4 (C), 51.4 (CH_3), 51.2 (CH_3), 39.7 (CH), 19.5 (CH_3), -0.5 (TMS); *Anal.* Calcd for $C_{21}H_{24}N_2O_6Si$: C, 57.86; H, 5.65; N, 6.54. Found: C, 58.18; H, 5.59; N, 6.62.
    To this solid (**14**) (1.5 mmol) in 10 mL of dry methanol was added 0.4 g (3 mmol) of K_2CO_3. After 10 min of reaction at room temperature, the solvent was removed under *vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ (2x5 mL), water (2x10 mL), separated, dried over $MgSO_4$ and concentrated to give after recrystallisation from a mixture of ligroin/ethyl acetate (3/4) the desired product (**3**) (75 to 95% yield) as a solid.
    Selected data for dimethyl 2-ethynyl-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3a**): Yield=89%; mp 183-185°C; IR: 3346 (NH), 3076 (=CH), 2945 (CH), 3248, 2117 (C≡C-H), 1686 (CO), 1651 (C=C), 1528, 1344 (NO_2), 1227 (COC); MS (EI, 70 ev) *m/z*: 356 (7, M^+), 339 (10), 287 (10), 235 (15) 234 (100); ^{1}H-NMR ($CDCl_3$): δ 8.11 (t, *J*=1.9 Hz, 1H, <u>H</u>$_8$-Ar), 8.03 (d, *J*=7.8 Hz, 1H, <u>H</u>$_{10}$-Ar), 7.64 (d, *J*=7.7 Hz, 1H, <u>H</u>$_{12}$-Ar), 7.41 (t, *J*=7.9 Hz, 1H, <u>H</u>$_{11}$-Ar), 6.24 (s, 1H, N<u>H</u>), 5.18 (s, 1H, <u>H</u>$_4$), 3.71 (s, 3H, OC<u>H</u>$_3$), 3.66 (s, 3H, OC<u>H</u>$_3$), 3.48 (s, 1H, ≡C<u>H</u>), 2.40 (s, 3H, C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$): δ 167.1 (C=O), 165.7 (C=O), 148.4 (C), 148.1 (C), 145.7 (C), 134.2 (CH), 129.0 (CH), 127.0 (C), 122.8 (CH), 121.8 (CH), 111.7 (C), 101.8 (C), 85.5 (C), 76.9 (CH), 51.6 (CH_3), 51.3 (CH_3), 39.5 (CH), 19.5 (CH_3); *Anal.* Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.60; H, 4.40; N, 8.02.
15. The olefin geometry of products (**17c-e**) was established as *E* according to the NOE Difference experiments.