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On the Regiochemistry of the Alkylation of *tert*-Butyl N-[6-Butyl-1,2-dihydro-2-oxo-3-pyridylmethyl]carbamate: Precursor of a Series of Potent Angiotensin II Receptor Antagonists[1]

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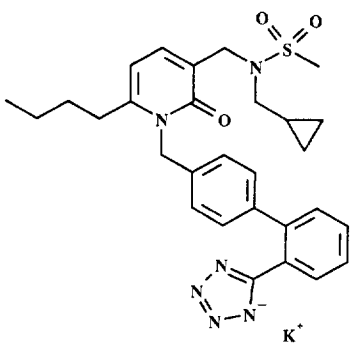
Abstract: The key intermediate **5** of a large number of potent AT_1 selective angiotensin II antagonists e.g. the potent cyclopropylmethyl derivative **1** (**EMD 69943**) was synthesized by regioselective alkylation of carbamate **3** with the well-known 4'-(bromomethyl)biphenyl-2-carbonitrile (**4**) and n-butyllithium as the preferred base.

Nonpeptide angiotensin II (Ang II) receptor antagonists are currently being investigated for treatment of cardiovascular disorders, including hypertension.[2] As part of our synthetic program aimed at Ang II antagonists, we identified 3-substituted 6-butyl-1,2-dihydropyridin-2-ones as potent AT_1 selective antagonists.[3] Among the substituents we introduced, sulfonamides were the most potent *in vitro*.[3] A promising compound with good *in vivo* results is cyclopropylmethyl derivative **1** (Figure 1, **EMD 69943**).[4]

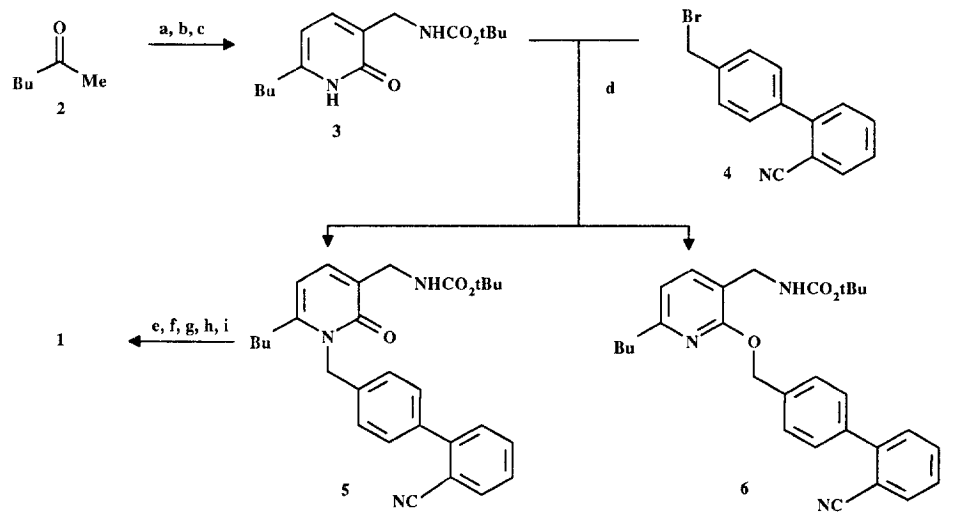
Figure 1:



EMD 69943

To further investigate the behaviour of this compound *in vivo*, we needed larger quantities of **1**. Therefore, an efficient preparation of **1** was required.

Scheme 1 describes the sequence of reactions which led to the preparation of the target molecule **1**. The crucial step within our original 10 step synthesis is the alkylation of pyridone **3** with 4'-(bromomethyl)biphenyl-2-carbonitrile (**4**), which gave rise to a mixture of N- and O-isomer **5** and **6**, respectively.[5] The key component **5** of the angiotensin II antagonist **EMD 69943** has been prepared from **3** in only 34% yield as the minor compound using potassium carbonate in dimethylformamide as a solvent (Table 1, entry 1). Since the low yield and the necessity of chromatography made this route less attractive for a large scale process, we searched for a superior alternative in this important step.



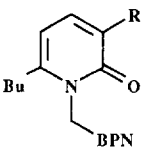
Scheme 1: Reagents: (a) HCO_2Et, 30proz. NaOMe in PhMe, rt, 3h, then $NCCH_2CONH_2$, H_2O/ HOAc/ piperidine (80/ 3/ 1), 100°C, 2h, (46%), (b) Raney Ni, 5 bar H_2, 10% NH_3 in MeOH, 30°C, 7h, (82%), (c) Boc_2O, Et_3N, CH_2Cl_2, 40°C, 1h, (85%), (d) n-BuLi, THF, -5 to 75°C, 73h, (92%), (e) 1M HCl, iPrOH, Δ, 2h, (84%), (f) $MeSO_2Cl$, Et_3N, PhMe, rt, 1h, (89%), (g) cyclo-$PrCH_2Cl$, K_2CO_3, $MeOCH_2CH_2OMe$, Δ, 72h, (98%), (h) NaN_3, $Et_3NH^+Cl^-$, NMP, Δ, 24h, (85%), (i) KOH, EtOH, rt, 1h, (92%).

Alkylation of an ambident anion such as 2-oxopyridine **3** is generally performed by treating the corresponding metal salt (S_E2cB mechanism) with an alkyl halide. The regioselectivity is influenced by the nature of the metal, the structure of the halide, substituents on the pyridone ring, the temperature, and the solvent.[6] Restricted by the substrate **3** and the corresponding electrophile **4** we focused our attention on the nature of the base, the counter-ion, and the solvent.

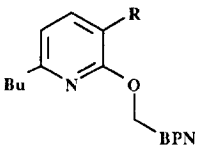
In a first study, we switched from the weak base, potassium carbonate, to the stronger base, potassium *tert*-butoxide. Although the N/O-ratio was positively influenced the major product was still the O-alkylated derivative **6** (Table 1, entry 2). Next, we examined the coupling of **3** with **4** under phase transfer conditions. Stirring both compounds with tetrabutylammonium iodide in a two phase system of sodium hydroxide and toluene we obtained predominantly N-alkylation (Table 1, entry 3). This was a great step forward, but does not overcome the upscale problem. Therefore we looked for another method.

The N-*tert*-butyloxycarbonyl (Boc) group has been shown to be a useful directing group under lithiation conditions.[7] We applied this methodology to carbamate **3** in order to improve the regioselectivity ratio. Carbamate **3** was reacted with one equivalent n-butyllithium in tetrahydrofuran to generate the lithiated species, which was subsequently treated with alkylating agent **4** to give the N-isomer **5** in 92% isolated yield (Table1, entry 4). This approach could be enlarged to a multi-gram scale without any problems giving the desired product **5** in an isolated yield of 87%.[8] The O-alkylated product **6** was only produced in traces and could be easily separated by crystallization. This outcome is strongly linked to the carbamate moiety. This could be shown by alkylation of the 3-cyano-2-oxopyridine analogue of compound **3**, which gave the desired N-isomer in good yield employing phase transfer conditions (Table 1, entry 5) but no considerable amount of product could be isolated in case of n-butyllithium (Table 1, entry 6).

Table 1: N- *vs.* O-alkylation of various 3-substituted 2-pyridones with 4'-(bromomethyl)biphenyl-2-carbonitrile



5[a]



6[a]

Entry	R	Base	Solvent	Yield [%][b]	
				5	**6**
1	CH_2NHCO_2tBu	K_2CO_3	DMF	34	63
2	CH_2NHCO_2tBu	KO*t*Bu	DMF	36	42
3	CH_2NHCO_2tBu	TBAI[c]	NaOH, PhMe	59	24
4	CH_2NHCO_2tBu	n-BuLi	THF	92	-
5	CN	TBAI	NaOH, PhMe	69	23
6	CN	n-BuLi	THF	-	-

[a] BPN = biphenyl-2-carbonitrile. [b] isolated yields. [c] TBAI = tetrabutylammonium iodide.

In summary, lithiation of the N-*tert*-butyloxycarbonyl pyridone **3** and alkylation of the lithiated species provides the N-alkylated intermediate **5** highly regioselective. This method, however, depends strongly on the nature of substituents in the 3-position of the 2-oxopyridone.

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References and Notes:

1. Dedicated to Prof. Dr. Hans-Joachim Langmann on the occasion of his 70th birthday

2. Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149.

3. Osswald, M.; Mederski, W. W. K. R.; Schwarz, M.; Beier, N.; Lues, I.; Minck, K.-O. *BioMed. Chem. Lett.* **1994**, *4*, 683.

4. 95% inhibition of Ang II induced increase in diastolic blood pressure in pithed rats (3 mg/kg, i.d.). For experimental details see Wong, P. C.; Price, W. A.; Chiu, T. A.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 790.

5. The structures of compounds **5** and **6** were unequivocally assigned by observations of nuclear Overhauser effects on the basis of ROESY spectra; compare Mederski, W. W. K. R.; Pachler, K. G. R. Tetrahedron **1992**, *48*, 10549.

6. For recent references, see: (a) Almena, I.; Diez-Barra, E.; de la Hoz, A. *Synth. Commun.* **1994**, *24*, 1057. (b) Comins, D. L.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 2819 and references cited therein.

7. Snieckus, V.; Rogers-Evans, M.; Beak, P.; Lee, W. K.; Yum, E. K.; Freskos, J. *Tetrahedron Lett.* **1994**, *35*, 4067 and references cited therein.

8. Large scale procedure for the preparation of **5**: To a stirred solution of **3** (280.4 g, 1.0 mol) in anhydrous THF (1.5 L) was added n-BuLi (427.0 g of a 1.5 M solution in hexane, 1.0 mol) at -5°C over 5 min. Then a solution of 4'-(bromomethyl)biphenyl-2-carbonitrile (**4**, 72.1 g, 1.0 mol) in anhydrous THF (1.5 L) was added to the reaction mixture at -5°C. The solution was allowed to warm to ambient temperature and subsequently refluxed for 72 h. The bright yellow solution was cooled to ambient temperature, quenched with water (4.0 L) and stirred for 30 min. The aqueous layer was separated and extracted with ethyl acetate (4 x 500 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed *in vacuo* to give an oil. The crude product was dissolved in *tert*-butyl methyl ether (5.0 L) and stirred at 10°C for 15 h. The resultant precipitate was filtered, washed with *tert*-butyl methyl ether and dried to yield 364.0 g of **5** as a white solid. The filtrate was concentrated, dissolved in *tert*-butyl methyl ether (1.5 L) and cooled again. After 12 h a second crop of crystalline product (46.4 g) was gained to provide 410.4 g (87%) of **5** as a white solid, altogether. HPLC indicated, that there was some more product in the second filtrate, which could only be purified by means of chromatography on silica gel. **5**: mp 89-90°C; IR (KBr) 3420, 3340, 2220, 1712, 1650 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.93 (dd, J = 7.4 and 0.9 Hz, 1 H), 7.78 (td, J = 7.8 and 1.1 Hz, 1 H), 7.61-7.53 (m, 4 H), 7.25-7.21 (m, 3 H), 7.12 (t, J = 6.0 Hz, 1 H), 6.20 (d, J = 7.2 Hz, 2 H), 5.40 (sbr, 2 H), 3.96 (d, J = 6.0 Hz, 2 H), 2.57 (t, J = 7.5 Hz, 2 H), 1.51-1.44 (m, 2 H), 1.41 (s, 9 H), 1.33-1.25 (m, 2 H), 0.82 (t, J = 7.5 Hz, 3 H); MS (FAB), m/z = 472 (M^+). Anal. Calcd for $C_{29}H_{33}N_3O_3$: C, 73.8; H, 7.0; N, 8.9. Found: C, 73.8, H, 6.9, N, 8.8.

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