Tetrahedron Letters, Vol. 33, No. 39, pp. 5713-5716, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

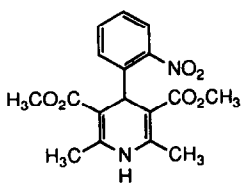
An Extremely Short Synthesis of Benzoylpyrrole-type Calcium Channel Activators

Christopher R. Dalton*, John M. Kane, and David Rampe

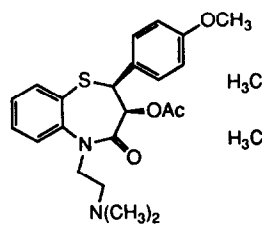
Marion Merrell Dow Research Institute
2110 E. Galbraith Road
Cincinnati, Ohio 45215

Abstract: Friedel-Crafts acylation of methyl 2,5-dimethylpyrrole-3-carboxylate with 2-chloromethylbenzoyl chloride generated the corresponding 4-(2-chloromethylbenzoyl)pyrrole which was reacted *in situ* with benzene and aluminum chloride to yield the novel calcium channel activator FPL 64176.

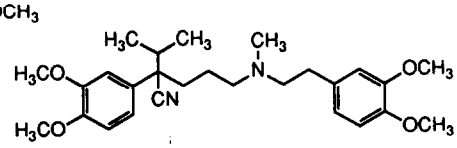
Voltage-dependent L-type calcium channels provide an important pathway for calcium influx into a variety of tissues. These channels are especially important in controlling excitation-contraction coupling in cardiac tissue and it is, therefore, not surprising that they are the target for a number of clinically important drugs, known collectively as the calcium channel antagonists.[1] These agents include the 1,4-dihydropyridines, typified by nifedipine (**1**), the benzothiazepines, typified by diltiazem (**2**), and the phenylalkylamines, typified by verapamil (**3**). While many compounds are known to act as antagonists of L-type calcium channels[2], only a few compounds are known to act predominately as L-channel activators.[3] These agents are structurally related to the 1,4-dihydropyridines and include compounds such as (S)-Bay K 8644 (**4**).[4] Recently, a novel 4-benzoylpyrrole derivative, FPL 64176 (**5**), was described as a potent activator



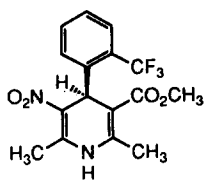
1



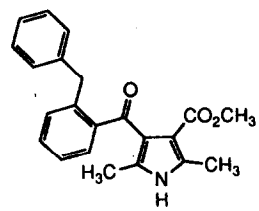
2



3



4

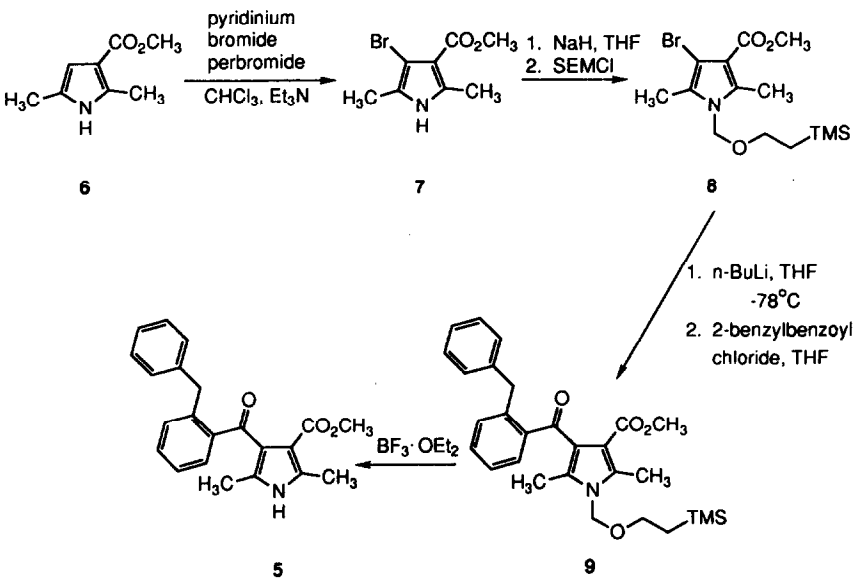


5

of L-type calcium channels.[5-7] Given our long-standing involvement with agents which effect L-type calcium channels, we wished to examine **5** in more detail. This letter describes a new two-step, one-pot synthesis of **5** which is amenable to the preparation of substituted analogs.

The previously reported synthesis of FPL 64176 (**5**) involved several steps. More specifically, bromination of methyl 2,5-dimethylpyrrole-3-carboxylate (**6**) afforded 4-bromopyrrole **7** which was protected as its 2-(trimethylsilyl)ethoxymethyl (SEM) derivative **8**. Halogen-metal exchange using n-butyllithium and acylation of the resulting carbanion then yielded 4-(2-benzylbenzoyl)pyrrole **9**. Deprotection of the pyrrole nitrogen with boron trifluoride etherate completed the synthesis of **5**[8] (Scheme 1).

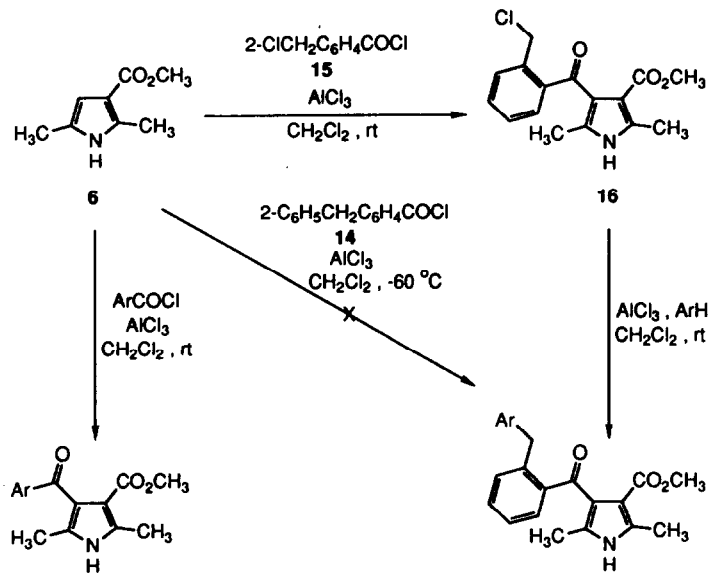
Scheme 1



The above procedure relied on a carbanion-mediated process for appending the 2-benzylbenzoyl substituent. Alternatively, if this transformation could be accomplished *via* a cation-mediated process, the need for a protection/ deprotection sequence should be negated. For example, pyrrole **6**, which is easily prepared *via* the reaction of methyl acetoacetate, chloroacetone, and ammonia, readily underwent Friedel-Crafts acylation at the 4-position in preference to acylation on nitrogen. In this manner, we have prepared several simple 4-benzoylpyrrole derivatives **10-13**[9] in 77-87% yield (Scheme 2). Unfortunately these derivatives were only weakly active as calcium channel activators, thus apparently emphasizing the importance of the 2-benzylbenzoyl substituent for calcium agonist activity. We next attempted to prepare **5** *via* the Friedel-Crafts acylation of **6** with 2-benzylbenzoyl chloride (**14**). As we expected, **14** underwent preferential intramolecular acylation yielding anthrone as the major product. Not wishing to abandon a Friedel-Crafts-based procedure, we modified our synthesis so as to eliminate the possibility for intramolecular acylation. Thus, Friedel-Crafts acylation of **6** with 2-chloromethylbenzoyl chloride (**15**)[10], readily obtained from the reaction of phthalide and dichlorotriphenylphosphorane, gave 4-(2-chloromethylbenzoyl)pyrrole **16**

in 58% yield (Scheme 2). Although pyrrole **16** could be isolated and characterized by NMR[11], it proved to be rather unstable and it was therefore immediately reacted with excess benzene and an additional equivalent of aluminum chloride affording **5** in 69% yield. In order to circumvent the instability of **16**, we have now found that the entire acylation/ alkylation sequence may be accomplished by a one-pot procedure which substantially improves the yield. Thus, generation of **16** *in situ*, followed by the addition of an additional equivalent of aluminum chloride and excess benzene afforded **5** in 60% overall yield from **6**. Using this one-pot procedure we have prepared derivatives **17-19** in 53-68% yield using fluorobenzene, 1,4-difluorobenzene, and toluene respectively.[12] In the reactions of both fluorobenzene and toluene, we observed approximately a 25:75 mixture of *ortho:para*-isomers following chromatography. In both cases, the *para*-isomers were selectively obtained after crystallization.

Scheme 2



		Yield
10	Ar = 4-ClC_6H_4	82%
11	Ar = 2,4-$Cl_2C_6H_3$	83%
12	Ar = 2-FC_6H_4	77%
13	Ar = 2-$CH_3OC_6H_4$	87%

		Yield
5	Ar = C_6H_5	60%
17	Ar = 4-FC_6H_4	63%
18	Ar = 2,5-$F_2C_6H_3$	53%
19	Ar = 4-$CH_3C_6H_4$	68%

In conclusion, we have developed a new, two-step, one-pot procedure for preparing FPL 64176 (**5**). This method is also amenable to the preparation of substituted analogs of this interesting L-channel agonist. The entire acylation/ alkylation sequence may be run on a multigram scale in 1-2 hours. Unlike the original synthesis, this method does not require a protection/ deprotection sequence and does not require either inert atmosphere techniques or low temperatures. Biological evaluation of the benzoylpyrroles prepared in this study revealed that pyrroles **10-13** displayed no activity at concentrations below 10^{-6} molar as determined by

their effect on potassium ion-dependent calcium influx in GH_3 cells. On the other hand, compounds **5** and **17-19** were more effective calcium channel agonists with EC_{50} values ranging from 10^{-7}-10^{-6} molar.[13]

References and Notes

1. Janis, R.A.; Silver, P.J.; Triggle, D.J. *Adv. Drug Res.* **1987**, *16*, 311-591.
2. Rampe, D.; Triggle, D.J. *Trends Pharmacol. Sci.* **1990**, *11*, 112-115.
3. Triggle, D.J.; Rampe, D. *Trends Pharmacol. Sci.* **1989**, *10*, 507-511.
4. Schramm, M.G.; Towart, T.R.; Franckowiak, G. *Nature (Lond.)* **1983**, *303*, 535-537.
5. McKechine, K.; Killingback, P.G.; Naya, I.; O'Conner, S.E.; Smith, G.W.; Wattam, D.G.; Wells, E. Whitehead, Y.M.; Williams, G.E. *Br. J. Pharmacol.* **1989**, *98*, 673P.
6. Zheng, W.; Rampe, D.; Triggle, D.J. *Mol. Pharmacol.* **1991**, *40*, 734-741.
7. Rampe, D.; Lacerda, A.E. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 982-987.
8. Dixon, J.; Baxter, A.J.G.; Manners, C.N.; Teague, S. Eur. Pat. Appl. EP 300,688, 25 Jan. 1989; *Chem. Abstr.* **1989**, *111*, 115023n.
9. All of the products prepared in this study, with the exception of **16** which was unstable, were fully characterizd (C, H, and N; ± 0.4% of theoretical values, IR, MS, NMR).
10. Burton, D.J.; Koppes, W.M. *J. Org. Chem.* **1975**, *40*, 3026-3032.
11. Colorless gum which rapidly darkens upon standing or heating; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 2.42 (s, 3H), 3.22 (s, 3H), 5.00 (s, 2H), 7.24-7.65 (m, 4H), 8.80 (br s, 1H).
12. **Representative Procedure for the Preparation of 4-(2-benzylbenzoyl)pyrroles 5, and 17-19. Methyl 4-[2-(2,5-difluorobenzyl)benzoyl]-2,5-dimethylpyrrole-3-carboxylate (18).** To a stirred, room temperature mixture of 2-chloromethylbenzoyl chloride (1.24 g, 4.92 mmol), aluminum chloride (0.80 g, 6.0 mmol), and CH_2Cl_2 (5 mL) was added a solution of methyl 2,5-dimethylpyrrole-3-carboxylate (0.74 g, 4.83 mmol) in CH_2Cl_2 (11 mL). After 15 min, an additional portion of aluminum chloride (0.80 g, 6.0 mmol) was added, followed 10 min later by the addition of excess 1,4-difluorobenzene (10 mL, 97 mmol) and a final portion of aluminum chloride (0.80 g, 6.0 mmol). After stirring 10 min, the reaction was poured into water. The aqueous mixture was extracted with CH_2Cl_2 (3 x 150 mL). The organic extracts were combined, washed with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure. The resulting oil was purified by flash chromatography[15] (10% EtOAc/ CH_2Cl_2) and crystallization (MeOH) affording colorless prisms: 0.98 g (53%); mp 146-147 °C; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.43 (s, 3H), 3.18 (s, 3H), 4.31 (s, 2H), 6.80-7.03 (m, 3H), 7.16-7.40 (m, 4H), 8.34 (br s, 1H). Anal. Calcd for $C_{22}H_{19}F_2NO_3$: C, 68.92; H, 4.99; N, 3.65. Found: C, 68.72; H, 4.97; N, 3.91.
13. The EC_{50} value is defined as the half-maximal stimulation of potassium ion-dependent calcium uptake in GH_3 cells.[14]
14. Rampe, D.; Skattebøl, A.; Triggle, D.J.; Brown, A.M. *J. Pharmacol. Exp. Ther.* **1989**, *248*, 164-170.
15. Still, W.G.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

(Received in USA 29 May 1992)