Pergamon

Tetrahedron Letters 42 (2001) 7683–7685

TETRAHEDRON LETTERS

Solid-phase Friedel–Crafts acylation on polystyrene resins-synthesis of antiepiletic 1-aryl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones

Francesca Bevacqua,[a] Andrea Basso,[b] Rosaria Gitto,[a] Mark Bradley[b,*] and Alba Chimirri[a,*]

[a]*Dipartimento Farmaco-Chimico, Università di Messina, viale Annunziata 96168, Messina, Italy*
[b]*Department of Chemistry, University of Southampton, Highfield SO17 1BJ, Southampton, UK*

Received 11 July 2001; accepted 24 August 2001

Abstract—Friedel–Crafts acylation with various acyl chlorides of resin-bound 3,4-dimethoxyphenylacetate afforded resin bound ketones which, following treatment with hydrazine, were converted into the corresponding 2,3-benzodiazepines in good yields and purities. © 2001 Published by Elsevier Science Ltd.

The preparation and screening of combinatorial libraries has in recent years become an attractive method for the discovery of pharmaceutical lead compounds, with much of the work concentrated on exploring and exploiting the synthesis of heterocycles.[1] We report here the solid-phase synthesis of 1-aryl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones, which are potentially useful for the treatment of epilepsy. The key synthetic step was a Friedel–Crafts acylation reaction on a polystyrene supported substrate, an unusual solid-phase reaction due to the nature of the solid support.

Epilepsy is a pathological state of the central nervous system (CNS). It affects 1% of the world's population and at the present time clinically available drugs produce satisfactory seizure control in only 60% of patients. L-Glutamate, the major excitatory neurotransmitter in the CNS, plays an important role in the convulsant phenomena and Glutamate receptors (GluRs) are involved in fundamental processes such as neuronal development, learning and memory. However, excessive stimulation of GluRs can cause damage of neuronal tissue during ischemic episodes, epileptic seizures and other neurological diseases. Antagonists of one subset of GluRs, (AMPA [2-amino-3-(-hydroxy-5-methylisoxazol-4-yl)propionic acid] type receptors[2]) have shown promise in the prevention and treatment of a broad range of neurological diseases[3] and pharmacological studies have shown that a series of 2,3-benzodiazepine derivatives acting as non-competitive AMPA receptor antagonists are potentially useful for the treatment of epilepsy.[4] Some of these compounds are more potent, less toxic and longer lasting anticonvulsant agents than their analogue GYKI 52466.[5]

In this paper we report the first results of our study towards the solid-phase synthesis of 1-aryl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones for the potential treatment of epilepsy (Fig. 1).

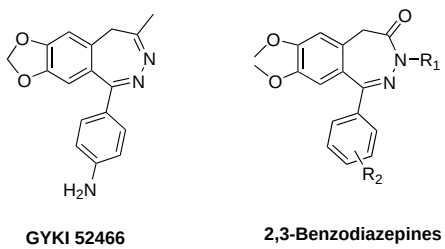


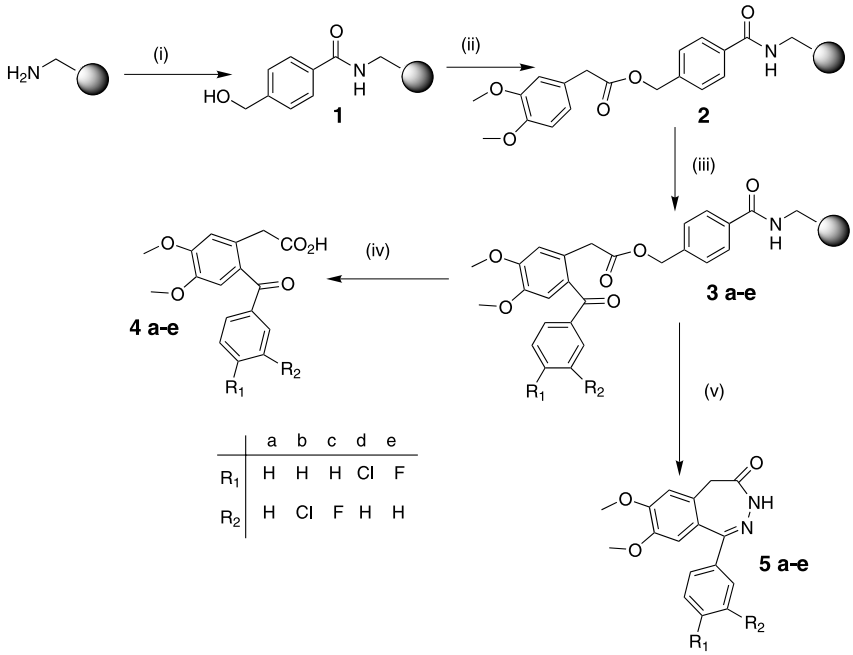
Figure 1. AMPA receptor antagonists.

The synthetic pattern followed is outlined in Scheme 1. The key steps were a Friedel–Crafts acylation of a resin-bound 3,4-dimethoxyphenylacetate and a concomitant hydrazine-mediated cleavage and ring closure. Given the reactivity of the polystyrene backbone, the Friedel–Crafts acylation reaction is not a routine solid-phase transformation and only few examples have been reported in the literature, most of which have been directed at modifications of the polystyrene backbone

Keywords: solid-phase synthesis; Friedel–Crafts acylation; 2,3-benzodiazepines.

* Corresponding authors. Fax +39 090 355613; e-mail: chimirri@pharma.unime.it

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)01602-1



Scheme 1. (i) 4-(Hydroxymethyl)benzoic acid (2 equiv.), DIC (2 equiv.), HOBt (2 equiv.), DCM, rt, 2 h ; then 1 M NaOH (aq)/dioxane 1:1, rt, 4 h; (ii) 3,4-dimethoxyphenylacetic acid (2 equiv.), DMAP (0.5 equiv.), DIC (2 equiv.), DCM, rt, 3 h; (iii) acyl chloride (1 equiv.), $SnCl_4$ or $FeCl_3$ (5 equiv.), DCM, rt, 6–12 h; (iv) 1 M NaOH (aq)/dioxane 1:1, rt, 4 h; (v) hydrazine (10 equiv.), EtOH, reflux, 24 h.

and not at the attached compound. For example Ajayaghosh and Pillai[6] reacted 2-nitrobenzoylchloride with polystyrene in the presence of $AlCl_3$ in dichloromethane (DCM) for the preparation of the photosensitive *o*-nitrobenzhydrylamino (NBHA) linker, Ferderigos[7] published an alternative method for the synthesis of high capacity aminomethyl polystyrene resin involving a Friedel–Crafts alkylation of polystyrene with *N*-(chloromethyl)phthalimide in the presence of $FeCl_3$, while in 1997 Park and Lee[8] tested a wide variety of Lewis acids for the alkylation of polystyrene with propylene oxide with $SnCl_4$ being the most effective.

Initially, hydroxymethyl polystyrene was used to directly attach 3,4-dimethoxyphenylacetic acid; however, difficulties were encountered, due to proximity of the resin backbone. Thus, as shown in Scheme 1, commercially available aminomethyl polystyrene resin (1% DVB, 1.2 mmol/g) was coupled with 4-(hydroxymethyl)benzoic acid using standard peptide coupling conditions, DIC/HOBt in DCM. This was then treated with 1 M NaOH (aq)/dioxane 1:1 to remove any linker oligomers formed via ester bond formation between the hydroxymethyl group and the benzoic acid, to give **1**.

3,4-Dimethoxyphenylacetic acid was esterified to the linker via the resin-bound hydroxymethyl group giving compound **2**. This was then quantitatively and selectively acylated with five different commercially available acyl chlorides: benzoyl chloride, 4-chlorobenzoyl chloride, 3-chlorobenzoyl chloride, 4-fluorobenzoyl chloride and 3-fluorobenzoylchloride. Acylation was performed in DCM at room temperature using the Lewis acids $FeCl_3$ or $SnCl_4$. No difference in reactivity, selectivity or purity of the resulting compounds **4** was observed upon varying the Lewis acid. Cleavage of compounds **3a–e** from the resin with hydrazine afforded the final benzodiazepines **5a–e** in good purity and isolated yields (Table 1), which were fully characterized.[9] In attempt to obtain the analogous alkyl derivatives, propionyl chloride was coupled onto resin **3**, but the resulting ketone **4** (obtained with 88% HPLC purity) did not give the desired benzodiazepine upon treatment with hydrazine. Fig. 2 shows the synthetic sequence in the synthesis of **5a**, and the high purity of the crude material.

In conclusion we have demonstrated how 2,3-benzodiazepines **5** can be straightforwardly synthesized on the solid-phase, using the Friedel–Crafts acylation on polystyrene supports. The cleavage/cyclization step using substituted hydrazines to generate a second source of diversity is now under investigation.

Table 1.

	4[a]	**5**[a,b]	
	HPLC purity (%)	HPLC purity (%)	Yield[c] (%)
a	91	81	62
b	91	67	36
c	77	27	32
d	86	57	29
e	40	41	27

[a] HPLC purity at 220 nm.
[b] Products were identified by ^1H NMR and MS spectroscopy.
[c] After semi-preparative HPLC purification.

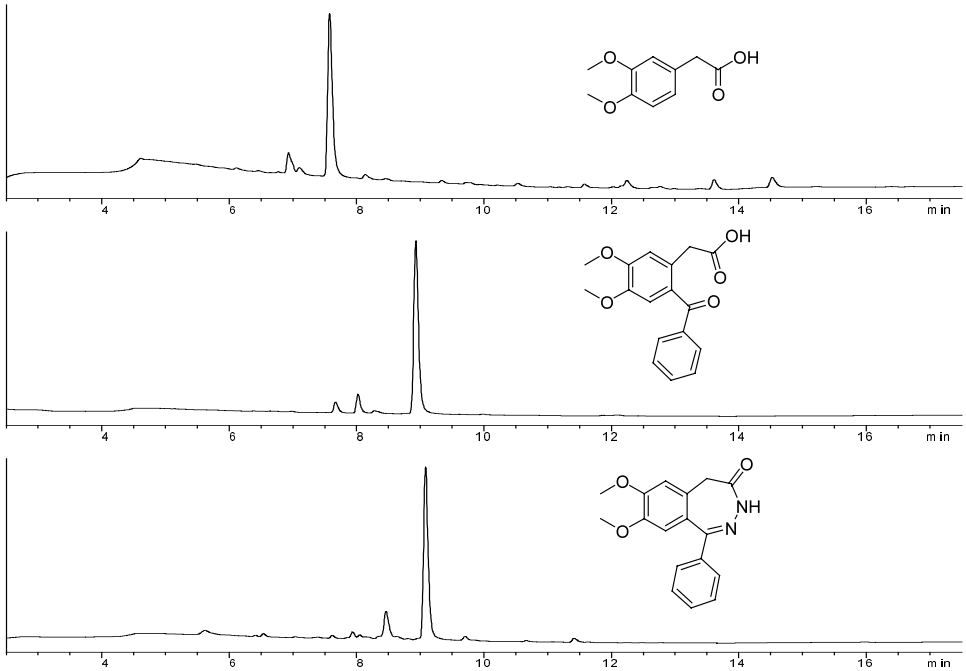


Figure 2. Crude HPLC traces of intermediates (**3a, 4a**) and benzodiazepine **5a** ($\lambda = 220$ nm).

Acknowledgements

Financial support for this research by Fondi di Ateneo di Ricerca (1998, Messina, Italy) is gratefully acknowledged. We also thank Sunil Rana for valuable proof reading.

References

1. (a) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17–42; (b) Booth, S.; Hermenks, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385–15443.
2. Dingledine, R.; Borges, K.; Bowie, D.; Traynelis, S. R. *Pharmacol. Rev.* **1999**, *51*, 7–61.
3. Chimirri, A.; Gitto, R.; Zappalà, M. *Exp. Opin. Ther. Patents.* **1999**, *9*, 557–570.
4. Chimirri, A.; De Sarro, G.; De Sarro, A.; Gitto, R.; Grasso, S.; Quartarone, S.; Zappalà, M.; Giusti, P.; Libri, V.; Costanti, A.; Chapman, A. *J. Med. Chem.* **1997**, *40*, 1258–1269.
5. Chimirri, A.; De Sarro, G.; De Sarro, A.; Gitto, R.; Quartarone, S.; Zappalà, M.; Costanti, A.; Libri, V. *J. Med. Chem.* **1998**, *41*, 3409–3416.
6. Ajayaghosh, A.; Pillai, V. N. R. *Tetrahedron Lett.* **1995**, *36*, 777–780.
7. Zikon, C. C.; Ferderigos, N. G. *Tetrahedron Lett.* **1995**, *36*, 3741–3744.
8. Park, B.-D.; Lee, H.-I.; Ryoo, S.-J.; Lee, Y.-L. *Tetrahedron Lett.* **1997**, *38*, 591–594.
9. Data for **5b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.42 (s, 2H, CH_2), 3.65 and 3.89 (s, 3H, OCH_3-7 and OCH_3-8), 6.57 (s, 1H, H-6), 6.78 (s, 1H, H-9), 7.27–7.60 (m, 4H, Ar), 8.32 (brs, 1H, NH); ES-MS (ES^+): 331 (100%, $[M+H]^+$). Data for **5c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.46 (s, 2H, CH_2), 3.67 and 3.90 (s, 3H, OCH_3-7 and OCH_3-8), 6.59 (s, 1H, H-6), 6.78 (s, 1H, H-9), 7.29–7.51 (m, 4H, Ar), 8.36 (brs, 1H, NH); ES-MS (ES^+): 315 (100%, $[M+H]^+$). Data for **5e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.46 (s, 2H, CH_2), 3.68 and 3.92 (s, 3H, OCH_3-7 and OCH_3-8), 6.58 (s, 1H, H-6), 6.79 (s, 1H, H-9), 7.12–7.63 (m, 4H, Ar), 8.48 (brs, 1H, NH); ES-MS (ES^+): 315 (100%, $[M+H]^+$). Data for **5a** and **5d** are consistent with the published literature.[4]