Pergamon

Tetrahedron Letters 41 (2000) 6993–6996

TETRAHEDRON LETTERS

Reactions of salicylaldehydes with alkyl cyanoacetates on the surface of solid catalysts: syntheses of 4*H*-chromene derivatives

Niefang Yu, James M. Aramini, Markus W. Germann and Ziwei Huang*

Kimmel Cancer Center, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA

Received 19 May 2000; revised 29 June 2000; accepted 30 June 2000

Abstract

Substituted 4*H*-chromene derivatives are a new class of compounds that bind Bcl-2 protein and induce apoptosis in tumor cells. Here we report an efficient synthetic method for the preparation of these compounds from salicylaldehyde derivatives and alkyl cyanoacetates under solid-phase catalysis. © 2000 Elsevier Science Ltd. All rights reserved.

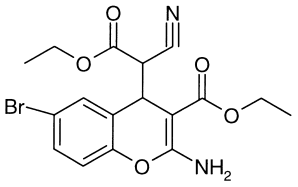
Keywords: 4*H*-chromene; cyclization; Bcl-Z protein; apoptosis; anti-cancer agents.

Bcl-2 and a family of related proteins regulate apoptosis or programmed cell death, and are implicated in a number of human diseases such as cancer.[1] Specifically, Bcl-2 can contribute to neoplastic cell expansion by preventing normal cell turnover caused by physiological cell death mechanisms. High levels of the Bcl-2 gene expression are found in a wide variety of human cancers and can lead to tumor cell resistance to conventional chemotherapy and radiotherapy.[2] Synthetic peptides that bind to a functional surface pocket of Bcl-2 have in vitro activity for inducing apoptosis in cell-free systems[3] and in HeLa cells.[4] Furthermore, Bcl-2 binding peptides containing a fatty acid as a cell permeable moiety can induce apoptosis in vitro and have in vivo activity in slowing human myeloid leukemia growth in severe combined immunodeficient mice.[5] These studies suggest that peptides or other small molecular ligands targeted at the Bcl-2 surface pocket could have important clinical applications.

We have recently discovered an organic compound, **1** (HA14-1), that exhibits a binding activity for the surface pocket of Bcl-2 protein ($IC_{50} = 9$ μM) and induces apoptosis of tumor cells.[6] The discovery of this Bcl-2 binding compound provides a promising lead for the development of potential anti-cancer agents, and prompted us to undertake chemical synthesis of a series of modified analogs of **1** in order to study its structure–activity relationship and increase its potency.

* Corresponding author. Tel: 215 503-4564; fax: 215 923-2117; e-mail: zhuang@nana.jci.tju.edu

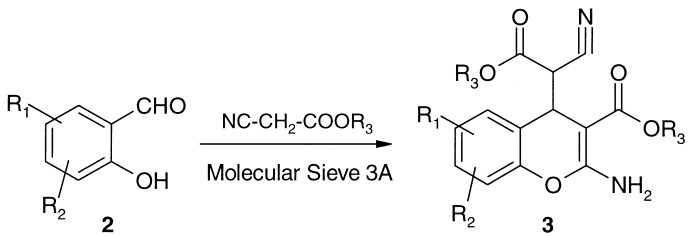
0040-4039/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)01195-3



1 (HA14-1)

Surprisingly, a survey of the literature revealed that the synthesis of the derivatives of **1** has received little attention in the past. To our knowledge, only two methods for the preparation of analogs of **1** have been reported. The first method developed by Fujimoto and Sakurai[7] involved the cyclization of salicylaldehyde derivatives with alkyl cyanoacetates in the presence of ammonium acetate at 5–10°C which gave derivatives of **1**. The reaction temperature (5–10°C) was crucial for obtaining the desired products. If the temperature was just slightly raised to 15–25°C, the reaction failed to give the desired product. In another procedure developed by Roudier and Foucaud,[8] aluminium oxide (Al_2O_3) was used as the catalyst instead of ammonium acetate and this approach has been applied in a limited number of examples.

Here we report an alternative procedure for the preparation of 4*H*-chromenes under mild conditions using molecular sieve 3A as the catalyst (Scheme 1). A typical reaction is as follow: To a suspension of the 5-bromosalicylaldehyde (0.010 mol) in dry ethyl alcohol (30 ml) was added ethyl cyanoacetate (0.022 mol) and 3.0 grams of molecular sieve 3A powder (Aldrich Chemical Company). The resulting mixture was stirred at room temperature overnight (14 h). Most of the 5-bromosalicylaldehyde disappeared within the first 2 h as determined by TLC. The molecular sieve was then filtered off and washed with tetrahydrofuran three times. The filtrate was combined and solvent was removed under vacuum. The residue solidified when cooled at –24°C for 2 h. The desired product was obtained by crystallization in 85% ethanol as a single diastereoisomeric pair. The yield was 86%.



Scheme 1.

Other types of molecular sieves, such as molecular sieves 4A and 5A, as well as Al_2O_3, were also compared using this procedure. All solid catalysts tested catalyzed the reactions, with type-3Å giving the best yields (Table 1). Table 2 summarizes several examples of the application of this new method using molecular sieve 3A. In most cases, good to excellent yields were obtained.[9]

In summary, we have developed an alternative procedure for the synthesis of 4*H*-chromene derivatives. Our method features mild reaction conditions, generally high yields, and facile manipulation. This new method has been used to synthesize a series of analogs for investigating

Table 1
Comparison of various solid catalysts

	Yield of **3a**, %
Molecular sieve 3A	86.1
Molecular sieve 4A	56.5
Molecular sieve 5A	50.2
Alumnium Oxide (Al_2O_3)	62.9

Table 2
Preparation of 4*H*-chromene derivatives by using molecular sieve 3A

	R_1	R_2	R_3	Yield* %
3a (HA14-1)	6-Br	H	$-CH_2CH_3$	86.1
3b	6-Br	H	$-C(CH_3)_3$	82.5
3c	6-Br	H	$-CH_2Ph$	60.0
3d	6-Br	H	$-CH_2CH_2OCH_3$	74.6
3e	6-Cl	H	$-CH_2CH_3$	70.7
3f	6-Cl	H	$-C(CH_3)_3$	74.8
3g	6-Cl	H	$-CH_2CH_2OCH_3$	72.9
3h	6-NO_2	H	$-C(CH_3)_3$	84.0
3i	H	8-$CH_2CH{=}CH_2$	$-CH_2CH_3$	78.1
3j	H	8-$CH_2CH{=}CH_2$	$-CH_2CH_2CH_2CH_3$	85.3
3k	5-Br	8-OCH_3	$-CH_2CH_3$	45.7
3l	6-NO_2	8-CH_2Br	$-CH_2CH_2CH_2CH_3$	51.3

*Isolated yield, without optimization

the structure–activity relationship of HA14-1 (manuscripts in preparation). The development of such a synthetic strategy should facilitate efforts in further lead optimization and drug development.

Acknowledgements

This work was supported by grants from the American Cancer Society and the Sidney Kimmel Foundation for Cancer Research.

References

1. (a) Adams, J.; Cory, S. *Science* **1998**, *281*, 1322–1326. (b) Chao, D. T.; Korsmeyer, S. J. *Annu. Rev. Immunol*. **1998**, *16*, 395–419. (c) Thompson, C. B. *Science* **1995**, *267*, 1456–1462.
2. Reed, J. C. *Curr. Opin. Oncol*. **1999**, *1*, 68–75.
3. Cosulich, S. C.; Worrall, V.; Hedge, P. J.; Green, S.; Clarke, P. R. *Curr. Biol*. **1997**, *7*, 913–920.
4. Holinger, E. P.; Chittenden, T.; Lutz, R. J. *J. Bio. Chem*. **1999**, *274*, 13298–13304.
5. Wang, J. L.; Zhang, Z. J.; Choksi, S.; Shan, S.; Lu, Z.; Croce, C. M.; Alnemri, E. S.; Korngold, R.; Huang, Z. *Cancer Res*. **2000**, *60*, 1498–1502.

6. Wang, J. L.; Liu, D.; Zhang, Z.; Shan, S.; Han, X.; Srinvasula, S. M.; Croce, C. M.; Alnemeri, E. S.; Huang, Z. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 7124–7129.
7. Fujimoto, A.; Sakurai, A. *Synthesis* **1977**, 871–872.
8. Roudier, J. F.; Foucaud, A. *Synthesis* **1984**, 159–160.
9. Data for **3a**: ^{1}H NMR (600 MHz, DMSO-d_6, δ): 1.33 (3H, t, J = 7.11 Hz, -CH_3), 1.35 (3H, t, J = 7.12 Hz, -CH_3), 3.98 (1H, d, J = 3.52 Hz, aliphatic-H), 4.28 (3H, q, J = 7, 12 Hz, -OCH_2Me and -OCH-Me), 4.33 (1H, m, -OCHMe), 4.68 (1H, d, J = 3.52 Hz, aliphatic-H), 6.10–6.90 (2H, b, -NH_2), 6.98 (1H, d, J = 8.70 Hz, aromatic-H), 7.26 (1H, d, J = 2.30 Hz, aromatic-H), 7.41 (1H, dd, J = 2.30, 8.70 Hz, aromatic-H). IR (cycles/cm^{-1}): 1710, 1725, 1745. MS calculated for $C_{17}H_{17}BrN_2O_5$: 409.24; found: 410 (M^+ +1).