Bromoalkoxy Addition on N-Azolyl Olefins

René Beugelmans,* André Lechevallier, Tawfik Gharbaoui, Thierry Frinault, and Rachid Benhida
Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France

(Received November 11, 1994)

N-Azolyl olefins undergo a cohalogenation reaction when treated by the NBS/ROH system to give novel N-(bromoalkoxypropane) azolyl derivatives.

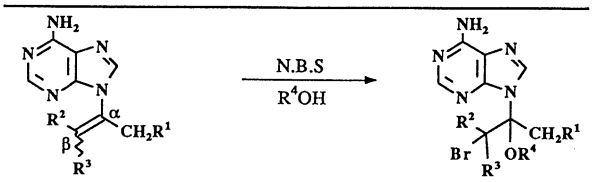
The bromoalkoxy addition reaction [1] which is related to similar E^+/Nu^- reactions of cyanogen bromide,[2] chloramine T,[3] aryl sulfonyl peroxide,[4] on enamines[5] provides a synthetically useful access to adenine derivatives of interest as precursors for compounds of potential biological activity.[6] A recent report dealing with bromo alkoxy addition on N-9-(3-hydroxypropenyl)adenine,[7] prompts us to publish now the results of studies effected on isomeric N-9-vinyladenine derivatives as well as N-vinylimidazole which became available in our laboratory.[8]

Treatement of enamine like olefins **1a-d**, with the N-bromosuccinimide/alcohol system (Table 1) led to the expected bromoalkoxy derivatives **3-8**.[9] The reaction of **1a** with the NBS/MeOH system led to **3**, while replacing this alcohol by glyceroformol **2b** gave the corresponding compound **4** in lesser yield. In contrast, the N-9-vinyladenine derivative **1b** reacted efficiently with methanol to give **5** in good yield.

The derivative **1c** (mixture of *Z* and *E* isomers) whose vinylic bond is part of a complex enamine like enol-ether function gave satisfactory yields of compounds **6** or **7** when reacted with the NBS/**2a** or **2b** system. The reactivity of **1c** with the NBS/**2b** system is twice as high than that of **1a**, presumably because the higher degree of substitution of the vinyl chain is balanced by an increase in electron density. The more highly functionalized **1d** (mixture of *Z* and *E* isomers) reacted with the NBS/**2a** system to give **8**, but from the N-9-vinyladenine derivative **1e**, whose β position is substituted by two methyl groups (tetrasubstituted olefin) the bromoalkoxy addition product **9** was not obtained.

The 6-aminopyrimidine portion of N-9-vinyladenine derivatives is not necessary for this reaction to take place as shown by formation of **10** issued from treatement of N-vinylimidazole **1f** with the NBS/MeOH system (Table 2). Furthermore, the range of alcohols used as nucleophilic agents also includes benzylalcohol **2c**, and glycol **2d** which afford respectively the imidazole compounds **11** and **12**.

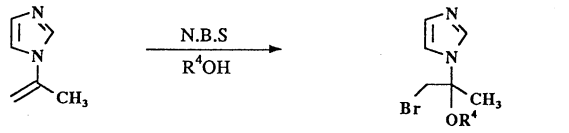
Table 1. Bromoalkoxy Addition on N-9-Adenyl Olefins



	R^1	R^2	R^3		R^4	Products (%)[a,b]
1a	H	H	H	2a	CH_3	3 (51)
	H	H	H	2b		4 (30)
1b	OTHP	H	H	2a	CH_3	5 (75)
1c	H	OTHP	H	2a	CH_3	6 (47)
	H	OTHP	H	2b		7 (60)
1d	OTHP	OTHP	H	2a	CH_3	8 (45)
1e	H	CH_3	CH_3	2a	CH_3	9 (0)

[a]Pure isolated products. [b]Oil; M.S. and NMR data in accord with the structure (ref. 9).

Table 2. Bromoalkoxy Addition on N-Vinylimidazole



	R^4	Products (%)[a,b]
1f	2a CH_3	10 (65)
	2c $PhCH_2$	11 (63)
	2d $HOCH_2CH_2$	12 (58)

[a]Pure isolated products. [b]M.S. and NMR data in accord with the structure (ref. 9).

Hence, it can be inferred that the bromoalkoxy addition is a general and useful reaction for functionalization of N-azolyl trisubstituted olefins.

References and Notes

1 J. Rodriguez and J.P. Dulcere, *Synthesis*, **1993**, 1179.
2 H. Ahlbrecht and D. Liesching, *Synthesis*, **1977**, 495.
3 I. Dyong and L.C. Quan, *Angew. Chem., Int. Ed.*, **18**, 933 (1979).
4 R. V. Hoffman, C. S. Carr, and B. C. Jankowski, *J. Org. Chem.*, **50**, 5148 (1985).
5 P. W. Hickmott, *Tetrahedron*, **38**, 1982 (1975).
6 J.L. Kelley, M.P. Krochmal, J.A. Linn, Ed.W. McLean and F. Soroko, *J. Med. Chem.*, **31**, 606 (1988).
7 M. Jokic and V. Skaric, *Tetrahedron Lett.*, **35**, 2937 (1994).
8 N-Azolyl olefins used in this study were synthesized by means of $S_{RN}1$ chemistry.
1a-e: T. Gharbaoui, R. Benhida, J. Chastanet, A. Lechevallier, P. Maillos and R. Beugelmans, *Bull. Soc. Chim. Fr.*, **131**, 561 (1994).
1f: unpublished results from T. Frinault's thesis, Université Paris XI (centre Orsay), March 5th 1990.
9 General procedure: A solution of N-azolyl olefins **1a-f** (1 eq.) in alcohol **2a-d** (5 ml) and N-bromosuccinimide (1.2 eq.) was stirred at room temperature untill completion of the reaction (20 to 60 min. TLC monitoring). The solution was then poured into water (50 ml) and extracted by methylene chloride (2x50 ml). The organic layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure to give a residual oil which was purified by silica gel column chromatography (elution: methylene chloride/methanol; 95/5).
Selected examples are:
3: oil. ^{1}HNMR ($CDCl_3$/200Mz); δ ppm: 2.15 (s, 3H), 3.38 (s, 3H), 3.98 (d, 1H, J = 11Hz), 4.28 (d, 1H, J = 11Hz), 6.18 (br. s, 2H, NH2), 8.02 (s, 1H, H_8 purine), 8.35 (s, 1H, H_2 purine). M.S. (CI): 288 $(MH)^+$, 153 (MH-adenine)$^+$, 136 (adenine + H)$^+$.
5: wite powder, mp: 81°C. ^{1}HNMR ($CDCl_3$/200Mz); δ ppm: 1.95 (s, 3H), 3.19 (m, 1H), 3.52 (m, 1H), 3.60 (s, 2H), 3.70 (m, 2H), 4.18 (br. s, 1H), 7.01 (s, 1H), 7.06 (s, 1H), 7.63 (s, 1H). M.S. (CI): 251 $(MH)^+$, 169 (MH-HBr)$^+$, 69 (imidazole + H)$^+$. Anal. Calc. for $C_8H_{13}O_2N_2Br$: C, 38.55; H, 5.22; N, 11.44. Found: C, 38.53; H, 5.12; N, 11.41.