Pergamon

Tetrahedron Vol. 51, No. 4, pp. 1069-1076, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)00998-8

Addition Reactions of Immonium Benzotriazolates To Acetylenic Esters

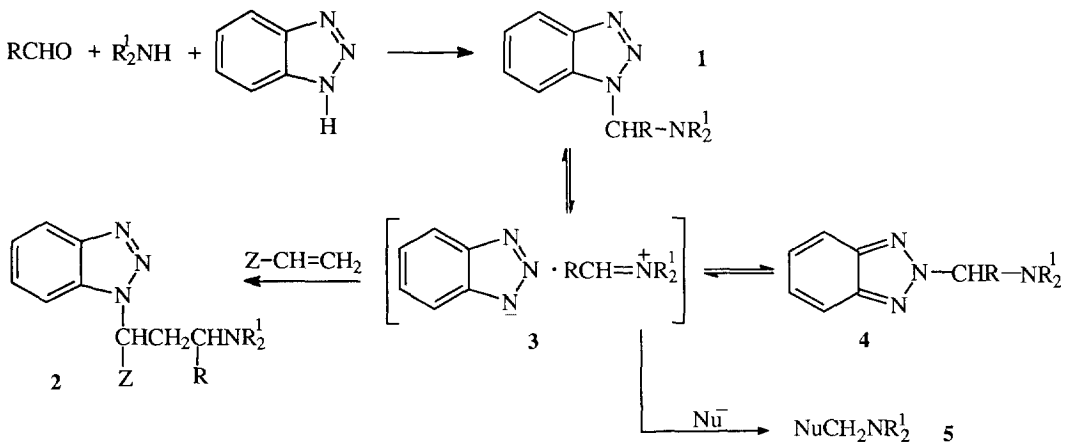
Alan R. Katritzky*, Clara N. Fali, and Daniela C. Oniciu

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA

Abstract: 1-Dialkylaminomethylbenzotriazoles react with ethyl propiolate and dimethyl acetylenedicarboxylate by addition of the benzotriazole anion followed by the immonium cation. The benzotriazolyl group in the products undergoes facile nucleophilic displacement.

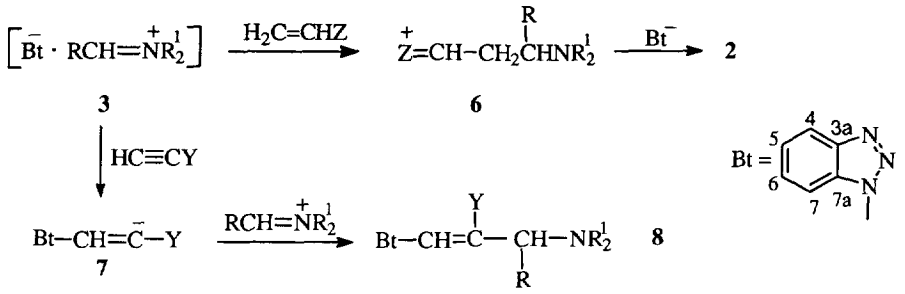
INTRODUCTION

Compounds of type **1**, readily formed by the condensation of an aldehyde, a secondary amine and benzotriazole[1,2], undergo reversible dissociation. An equilibrium with a finite quantity of ion pairs **3**[3,4] is established, which mediates the tautomerism in solution with the isomeric species **4**[5]. Compounds of type **1** are valuable synthetic intermediates and react with a wide variety of simple nucleophiles to give products **5**, in which the benzotriazolyl group has been replaced[6]. Recently we described addition reactions of **1** with electron rich olefins (vinylamines[7] and vinyl ethers[5]) to give addition products **2** (Scheme 1).



Scheme 1

In the formation of **2**, the first step is undoubtedly addition of the immonium cation from **3** to the electron rich olefin to give **6**. We now demonstrate that a stepwise reaction in the opposite sense is possible for certain electron deficient acetylenes with the formation of **8** *via* intermediate **7** (Scheme 2).



Scheme 2

The addition of nucleophiles followed by H^+ to electron-deficient double bonds is the familiar Michael reaction[8,9]. However, examples in which the product from nucleophilic addition to an electron-deficient C=C subsequently adds a carbon electrophile are rare, although the familiar nucleophilic-induced polymerization of electron-deficient olefins[10,11] falls into this category. Several studies on the addition of amines to acetylenic esters have been reported[12-16], giving both the *trans* and *cis* isomers, depending on the reaction conditions and the steric nature of the amine[9]. Addition of alcohols similarly gives both the *trans* and *cis* enol ethers[9]. We now show that successive addition of the benzotriazole anion and the immonium cation can occur in electron deficient acetylenes.

RESULTS AND DISCUSSION

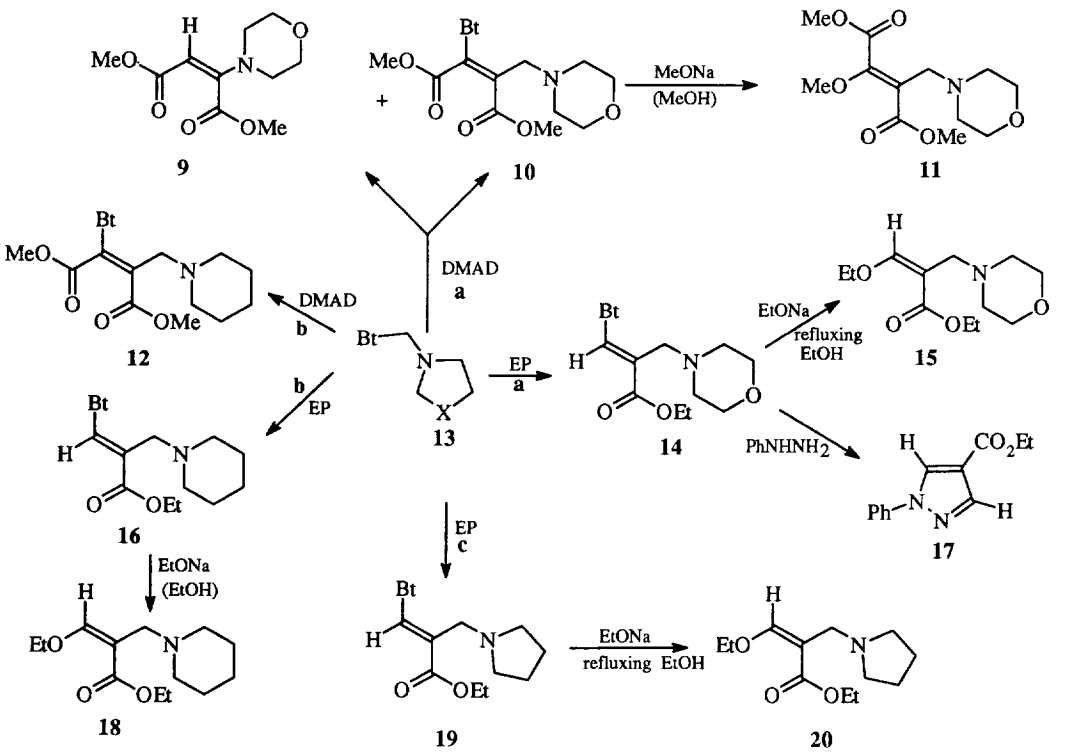
Reactions of Dimethyl Acetylenedicarboxylate (DMAD).

The reaction of 1-(morpholinomethyl)benzotriazole (**13a**) with dimethyl acetylenedicarboxylate gave the adduct **10** (30%) together with dimethyl morpholinomaleate (**9**) resulting from a simple addition product of morpholine to dimethyl acetylenedicarboxylate. (The preparation of compound **9** has been previously reported[17]). Compounds **9** and **10** were separated by column chromatography (Scheme 3).

It was elucidated from the NMR spectra (Tables 1 and 2) and NOE experiments that structure **10** contains *cis*-carboxylate groups. When the singlet at 5.57 ppm (2H) was irradiated, a positive NOE occured at 3.35 ppm (t, 4H) and at 7.68 ppm (d, 1H), indicating a *cis* relationship between the 1-morpholinomethyl and the benzotriazole groups.

Similarly, **9** was shown to be the maleate isomer by a positive NOE on the alkenyl proton (4.53 ppm) when the protons of the morpholino group at 2.87 ppm were irradiated. When the two methyl groups (3.38 and 3.75 ppm) were irradiated a positive NOE at 4.53 ppm was observed only on irradiation of the 3.38 ppm methyl group (^1H and ^{13}C NMR data are given in the experimental section).

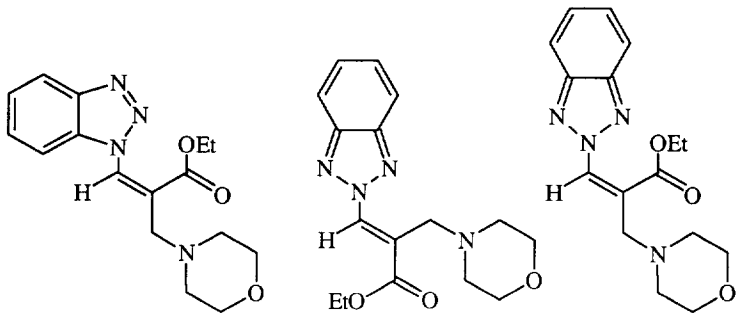
The reaction of 1-(piperidinomethyl)benzotriazole (**13b**) with dimethyl acetylenedicarboxylate gave the addition product **12**. The structure was assigned by ^1H and ^{13}C NMR.



EP = ethyl propiolate; DMAD = dimethyl acetylenedicarboxylate.

a : X = $-CH_2O-$; **b**: X = $-(CH_2)_2-$; **c** : X = $-CH_2-$

Scheme 3



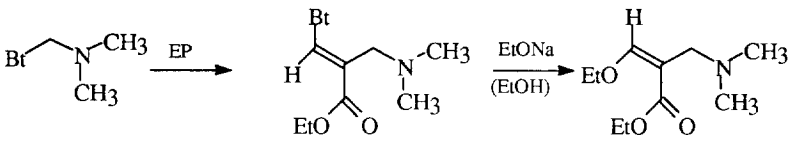
Scheme 4

Table 1. ^{1}H NMR Data for Compounds **10, 12, 14, 16, 19** and **25** (δ, ppm; J, Hz)

Compd	Bt - ring								2 (Me)	Et				CH_2	Others
	4(1H, d)		5(1H, t)		6(1H, t)		7(1H, d)		(3H, s)	CH_2(2H, q)		CH_3(3H, t)		(2H, s)	
	δ	J	δ	J	δ	J	δ	J	δ	δ	J	δ	J	δ	
10	8.04	8.8	7.36	8.8	7.49	8.8	7.68	8.8	3.60 3.82					5.57	3.35 (t, 4H) 3.72 (br, 4H)
12	8.02	8.0	7.40	8.0	7.46	8.0	7.68	8.0	3.59 3.85					5.59	1.35 (br, 6H) 3.35 (br, 4H)
14	8.02	8.0	7.33	8.0	7.34	8.0	7.75	8.0		4.18	7.0	1.22	7.0	5.65	3.67 (br, 4H) 3.72 (br, 4H) 7.75 (s, 1H)
16	7.95	8.0	7.35	8.0	7.58	8.0	7.69	8.0		4.12	6.8	1.18	6.8	5.64	1.65 (br, 6H) 3.60 (br, 4H) 7.25 (s, 1H)
19	8.02	8.0	7.38	8.0	7.45	8.0	7.82	8.0		4.12	6.7	1.23	6.7	5.62	1.90 (br, 4H) 3.72 (br, 4H)
25	8.02	7.8	7.32	7.8	7.45	7.8	7.80	7.8		4.15	6.0	1.23	6.0	5.69	3.25 (s, 6H) 7.65 (s, 1H)

Table 2. ^{13}C NMR Data for Compounds **10, 12, 14, 16, 19** and **25** (δ, ppm)

Compd	Bt - ring						CO_2	Me	Et		CH_2	Others
	3a	4	5	6	7	7a			CH_2	CH_3		
10	144.8	118.7	122.8	126.2	109.3	132.2	166.7 165.1	50.7 50.9			44.9	49.7 65.6 100.1 153.9
12	145.7	119.4	123.6	126.9	110.4	132.9	166.5 168.2	52.5 51.6			46.5	51.5 25.9 23.3 96.7 155.7
14	145.5	119.1	123.5	126.7	110.7	132.7	169.3		59.9	14.3	43.8	50.8 66.2 90.1 150.2
16	145.9	119.4	123.5	126.7	111.1	132.9	170.1		59.9	14.2	44.6	23.8 26.1 52.6 88.2 150.6
19	148.9	119.2	123.5	126.6	111.1	132.5	168.6		59.6	14.1	43.9	25.2 60.2 148.6 90.1
25	145.8	119.3	123.5	126.7	111.0	133.0	169.7		59.7	14.5	43.6	43.5 89.7 151.9



24 **25** **26**

Scheme 5

Reactions of Ethyl Propiolate.

1-(Morpholinomethyl)benzotriazole (**13a**) and ethyl propiolate in the presence of 1.2 equivalents of $ZnBr_2$ gave the addition product **14** in 80% isolated yield after 6 days. The structure of **14** (Scheme 3) was

assigned from the CHN analysis and NMR spectra (Tables 1 and 2). A positive NOE observed at 7.75 ppm (1H) when the signal at 5.65 ppm (2H) was irradiated indicates a *cis* relationship between the 1-morpholinomethylene group and the benzotriazole moiety.

However, the conversion of **13a** to **14** is more complex than a simple addition to a single product. The ^{1}H and ^{13}C spectra showed the presence of four isomeric products in the reaction mixture after 3 days. At this time, the ^{1}H NMR spectrum showed four singlets at δ 5.41 (2H), 5.56 (2H), 5.67 (2H) and 5.80 (2H), having intensities in the ratio 1 : 1.5 : 0.5 : 1, each corresponding to a methylene group adjacent to a double bond. The aromatic region showed the presence of both Bt^1 (benzotriazol-1-yl) (7.85-8.1, m; 7.6, t; 7.0-7.5, m) and Bt^2 (benzotriazol-2-yl) groups (7.70-7.8, m; 7.2-7.4, m). The ethoxy and morpholino signals appeared as multiplets as a result of overlap of peaks for the different isomers. Thus, at this stage of the reaction, product **14** is accompanied by **21**, **22** and **23** (Scheme 4). Compounds **21** - **23** are evidently formed under kinetic control and as the reaction proceeds the thermodynamically more stable **14** is ultimately formed essentially exclusively as evidenced by the nmr spectra of the reaction mixture.

Ethyl propiolate forms products **16** (57%) and **19** (54%) with 1-(piperidinomethyl)- (**13b**) and 1-(pyrolidinomethyl)-benzotriazole (**13c**). The structures, similar to that of **14**, were assigned similarly. By analogy, the reaction of benzotriazol-1-yl-*N*,*N*-dimethylmethane (**24**) with ethyl propiolate gave the addition product **25** (Scheme 5).

Transformations of Initial Adducts of Immonium Benzotriazolates and Acetylenic Esters.

The benzotriazole residues in the products are readily replaced by nucleophiles, as expected for an addition-elimination sequence. Thus, treatment of **14** with ethanolic sodium ethoxide gave ethoxy derivative **15.** Complete assignments for the proton and carbon chemical shifts of **15** were made on the basis of the proton-carbon direct couplings determined by HETCOR experiments. A positive NOE at 3.54 ppm was observed when the alkenyl proton (7.47 ppm) was irradiated, indicating a *cis* relationship between the alkenyl proton and the morpholino moiety. Treatment of **19** and **25** with ethanolic sodium ethoxide gave **20** and **26** respectively.

Compound **10** was similarly converted by MeOH-NaOMe to analog **11**. Phenylhydrazine displaced both the benzotriazole and morpholine groups in **14** to give **17.** The structure of **17** was assigned on the basis of the ^{1}H - ^{13}C direct couplings determined by HETCOR experiments. Similar syntheses of **17** have been described in the literature[18]).

Acknowledgment: We thank Dr. Ion Ghiviriga for discussions.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or on a Kofler hot-plate microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on either a Varian VXR 300 MHz or a Gemini 300 MHz spectrometer with tetramethylsilane as the internal standard. J values are given in Hz. The structures of compounds **9-17** were assigned using NOEDIF, INAPT and bi-dimensional NMR

experiments (COSY, HETCOR). Low resolution mass spectra were recorded on a Hewlett-Packard 5890 gas chromatograph, equipped with a flame ionization detector and a Hewlett-Packard 5972 mass selective detector. Compounds **13a-c** were prepared according to literature method[19].

Reactions of Diethyl Acetylenedicarboxylate.

a) With 1-(morpholinomethyl)benzotriazole (13a). DMAD (0.7 g, 0.7 mmol) was added to a solution of 1-(morpholinomethyl)benzotriazole (**13a**) in toluene (50 ml) at 40-60 °C. $ZnBr_2$ (0.07 g, 0.3 mmol) was added and the reaction maintained at 60-80 °C for 72 hours. The reaction was monitored by GC. The reaction mixture was cooled to room temperature and washed with water (3 x 50 ml), the organic layer separated, dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo*. The residue was recrystallized from ethanol to give a mixture of **9** and **10.** The two compounds were separated by flash column chromatography. The first compound eluted was **9** (eluent: methylene chloride), yield 30% . ^1H NMR: δ 2.87 (m, 4H), 3.38 (s, 3H), 3.48 (m, 4H), 3.75 (s, 3H), 4.53 (s, 1H); ^{13}C NMR: δ 47.06, 50.73, 52.75, 65.72, 87.00, 154.62, 167.57. HRMS (FAB) m/z = 230.1139 (m^+ + 1, 100%, $C_{10}H_{16}O_5N$ requires 230.1028). The second compound eluted was **10** (eluent: wet methylene chloride) which was further recrystallized from diethyl ether in 35% yield, mp 124 °C. Anal. Calcd. for $C_{17}H_{20}N_4O_5$: C 56.56, H 5.56, N 15.56. Found: C 56.30, H 5.57, N 15.46.

b) With 1-(piperidinomethyl)benzotriazole (13b). A mixture of 1-(piperidinomethyl)benzotriazole (**13b**) (1 g, 4.6 mmol) and DMAD (0.66 g, 4.6 mmol) in toluene (50 ml) at 40-60 °C was treated with $ZnBr_2$ (0.07 g). The temperature was maintained at 60-100 °C for 6 days. The reaction mixture was cooled, washed with water (3 x 50 ml), the organic layer separated, dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo*. The residue was treated with diethyl ether (5ml) to give **12** in 56% yield. HRMS (FAB) m/z =359.1576 (m^+ +1, 2.17%, $C_{18}H_{23}N_4O_4$ requires 359.1719)

Reactions of Ethyl propiolate.

a) With 1-(morpholinomethyl)benzotriazole (13a). A mixture of 1-(morpholinomethyl)benzotriazole (**13a**) (1.5 g, 7 mmol) and ethyl propiolate (0.7 g, 7 mmol) in toluene (50 ml) at 40-60 °C was treated with 1.2 equivalents of $ZnBr_2$ for 6 days. The reaction was monitored by GC. The reaction mixture was cooled, filtered, washed with water (3 x 50 ml), dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo*. The residue was treated with diethyl ether (5 ml) and the precipitate formed was filtered, washed with diethyl ether (50 ml) and dried to give **14** in 80% yield, mp 105 °C. Anal. Calcd. for $C_{16}H_{20}NO_4$: C 60.57, H 6.33, N 17.72. Found: C 60.76, H 6.33, N 17.85

b) With 1-(piperidinomethyl)benzotriazole (13b). A mixture of 1-(piperidinomethyl)benzotriazole (**13b**) (1.5 g, 6.8 mmol) and ethyl propiolate (0.67 g, 6.8 mmol) at 40-60 °C was treated with $ZnBr_2$ for 3 days. The reaction mixture was cooled to room temperature, filtered and washed with water (3 x 50 ml). The organic layer was dried (anhydrous $NaSO_4$) and the solvent removed *in vacuo*. The residue was treated with diethyl ether (5 ml) to give **16** in 50% yield. HRMS (FAB) m/z = 315.1828 (m^+ + 1, 23.7%, $C_{17}H_{23}O_2N_4$ requires 315.1821).

c) With 1-(pyrrolidinomethyl)benzotriazole (13c). A mixture of 1-(pyrrolidinomethyl)benzotriazole (**13c**) (1.5 g, 7.43 mmol) and ethyl propiolate (0.74 g, 7.4 mmol) at 40-60 °C was treated with $ZnBr_2$ for 3 days. The reaction mixture was cooled to room temperature, filtered and washed with water (3 x 50 ml). The organic layer was dried (anhydrous $NaSO_4$) and the solvent removed *in vacuo*. The residue was treated with

diethyl ether (5 ml) to give **19** in 20% yield. HRMS (FAB) m/z = 301.1750 (m^+ + 1, 2.33%, $C_{16}H_{21}O_2N_4$ requires 301.1660)

*d) With benzotriazol-1-yl-2-*N,N*-dimethylmethane (24).* To a solution of benzotriazol-1-yl-2-*N,N*-dimethylmethane (**24**) (1.5 g, 8.7 mmol) in toluene (50 ml) was added ethyl propiolate (0.86 g, 8.7 mmol) and $ZnBr_2$ (0.07 g). The mixture was maintained at 60-80 °C with stirring for 4 days. The reaction mixture was cooled, filtered, washed with water (3 x 50 ml), dried (anhydrous Na_2SO_4) and the solvent removed *in vacuo*. The residue was treated with diethyl ether (5 ml) to give **25** in 80% yield. HRMS (FAB) m/z = 275.1520 (m^+ + 1, 14.1%, $C_{14}H_{19}O_2N_4$ requires 275.1508).

Replacement of benzotriazole with sodium methoxide.

A solution of the benzotriazole adduct **10** (0.72 g, 2 mmol) in methanol (20 ml) was treated with sodium metal (0.07 g, 3 mmol), under reflux for 8-10 hours until no starting material was observed by GC. The mixture was cooled, poured into water and extracted with methylene chloride. The organic extract was washed with brine (2 x 50 ml) and dried (anhydrous Na_2SO_4). The solvent was removed *in vacuo* to give **11** in 98% yield. ^1H NMR: δ 3.3 (s, 3H), 3.42 (t, 4H), 3.68 (s, 3H), 3.70 (m, 4H), 3.85 (s, 3H), 4.14 (s, 2H); ^{13}C NMR: δ 50.2, 58.8, 62.9, 63.8, 66.1, 93.4, 150.0, 169.2.

Replacement of benzotriazole with sodium ethoxide.

A solution of the benzotriazole adduct **14** (0.64 g, 2 mmol) in ethanol (20 ml) was treated with sodium metal (0.07 g, 3 mmol) and the mixture heated under reflux for 8-10 hours, until no starting material was detected by GC. The reaction mixture was cooled, poured into water (150 ml) and extracted with methylene chloride. The organic extract was washed with brine (2 x 50 ml) and dried (anhydrous Na_2SO4). The solvent was removed to give **15** in 98% yield. ^1H NMR: δ 1.18 (t, 3H), 1.25 (t, 3H), 3.48 (q, 2H), 3.54 (t, 4H), 3.70 (dd, 4H), 3.79 (s, 2H), 4.14 (q, 2H), 7.47 (s, 1H); ^{13}C NMR: δ 14.0, 14.7, 50.2, 58.8, 63.8, 63.9, 66.1, 93.4, 150.0, 169.2. Anal. Calcd. for $C_{12}H_{21}NO_4$: C 59.25, H 8.64, N 5.76. Found: C 58.94, H 8.75, N 5.96.
Reaction of compound **16** with sodium ethoxide similarly gave **18** in 80% yield. ^1H NMR: δ 1.18 (t, 3H), 1.21 (t, 3H), 1.60 (br, 4H), 3.18 (br, 2H), 3.50 (br, 4H), 4.15 (q, 2H), 4.16 (q, 2H), 4.28 (s, 2H), 7.54 (s, 1H); ^{13}C NMR: δ 14.1, 15.1, 23.0, 26.4, 52.0, 52.3, 63.8, 63.9, 150.9, 151.9, 170.4. Similar treatment of **19** gave **20** in 60% yield. ^1H NMR: δ 1.28 (t, 6H), 1.95 (br, 4H), 3.52 (q, 2H), 3.6 (br, 4H), 4.15 (q, 2H), 4.3 (s, 2H), 7.72 (s, 1H); ^{13}C NMR: δ 14.5, 15.4, 25.3, 58.6, 59.1, 63.5, 64.5, 84.6, 148.5, 170.1. Treatment of **25** with sodium ethoxide gave **26** in 85% yield. ^1H NMR: δ 1.28 (t, 3H), 1.29 (t, 3H), 3.18 (s, 6H), 3.51 (q, 2H), 4.14 (q, 2H), 4.30 (s, 2H), 7.51 (s, 1H); ^{13}C NMR: δ 14.5, 15.3, 42.7, 59.2, 63.1, 64.4, 152.1, 170.2.

Reaction of benzotriazole adduct (14) with phenylhydrazine.

Compound **14** (0.64 g, 10 mmol) was treated with phenylhydrazine (0.12 g, 12 mmol) and heated to 100 °C for 10 hours until no starting material was detected by GC. The reaction mixture was extracted with diethyl ether (20 ml), and then with brine (3 x 50 ml). The organic layer was dried (anhydrous $NaSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed on alumina and eluted with methylene chloride to give compound **17** in 75% yield, mp 90-93 °C (lit.[18] mp 100 °C). ^1H NMR: δ 1.40 (t, 3H), 4.35 (q, 2H), 7.35 (t,

2H), 7.48 (t, 1H), 7.72 (d, 2H), 8.12 (s, 1H), 8.42 (s, 1H); ^{13}C NMR: δ 14.4, 29.7, 119.6, 127.5, 129.6, 129.7, 130.0, 142.2, 145.5, 168.0.

REFERENCES

1. Katritzky, A. R.; Drewniak, M. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2339-44
2. Katritzky, A. R.; Lan, X.; Zhang, Z. *J. Heterocycl. Chem.* **1993**, *30*, 381-87
3. Smith, J. R. L.; Sadd, J. S., *J. Chem. Soc. Perkin Trans. 1* **1975**, 1181-84
4. Katritzky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1993**, *58*, 812-13
5. Katritzky, A. R.; Gordeev, M. F. *J. Org. Chem.* **1993**, *58*, 4049-51
6. Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683-731
7. Katritzky, A. R.; Pernak, J.; Fan, W. Q. *J. Prakt. Chem.* **1992**, *334*, 114-118
8. Khetan, S. K.; George, M. V. *Tetrahedron* **1969**, *25*, 527-40
9. Winterfeldt, E. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 423-35
10. Frankel, M. ; Ottolenghi, A.; Albeck, M.; Zilkha, A. *J. Chem. Soc.* **1959**, 3858-63
11. Zilkha, A.; Feit, B.; Frankel, M. *J. Chem. Soc.* **1960**, 928-33
12. Krogsgaard-Larsen, P.; Brogger, C. S.; Hjeds, H. Acta Chem. Scand. 1973, *27*, 2802-12. *Chem. Abstr.* **1974**, *80* 59888a
13. Schmetzer, J.; Krenkler, K. P. Daub, J. *Tetrahedron Lett.* **1976**, 4061-4
14. Pocar, D.; Rossi, L. M.; Trimarco, P.; Vago, L. *J. Heterocycl. Chem.* **1980**, *17*, 881-5
15. Daub, J.; Hasenhuend, A.; Krenkler, K. P.; Schmetzer, J. *Liebigs. Ann. Chem.* **1980**, *7*, 997-1015. *Chem. Abstr.***1980** *93* 204820x
16. Souquet, F.; Martens, T.; Fleury, M.-B. *Synth. Comm.* **1993**, *23*, 817-828
17. Grinblat, E. I.; Postovskii, I. Ya. *Doklady Akad. Nauk S. S. S. R.* **1960**, *133*, 847-50. *Chem. Abstr.* **1960**, *54*, 24756i
18. Takamizawa, A.; Hayashi, S. *Japan Pat.* (**1959**), 5674. *Chem. Abstr.* **1964**, *54*, 14272a
19. Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Org. Prep. Proced. Int.* **1989**, *21*, 135-139

(*Received in USA* 21 *September* 1994; *accepted* 7 *November* 1994)