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BENZOTRIAZOL-1-YLMETHYL ISOCYANIDE, A NEW SYNTHON FOR CH-N=C TRANSFER. SYNTHESES OF α-HYDROXYALDEHYDES, 4-ETHOXY-2-OXAZOLINES AND OXAZOLES

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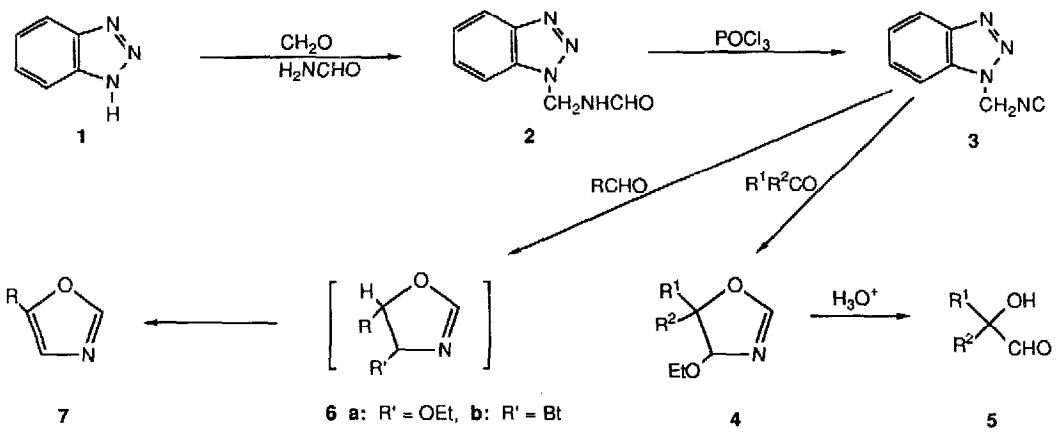
***Summary**: Readily prepared benzotriazol-1-ylmethyl isocyanide (BetMIC) reacts under mild conditions with ketones and aldehydes, to afford oxazolines (convertible into α-hydroxyaldehydes) and oxazoles, respectively.*

Since its first preparation,[1] tosylmethyl isocyanide (TosMIC) has become an important tool with widespread applications in the conversion of ketones to nitriles[2,3] and in the synthesis of various five-membered ring heterocycles.[4,5] The reactions of TosMIC depend strongly on the conditions used. Thus, it condenses with ketones under various conditions to give nitriles, 1-formylamino-1-tosylalkenes or 4-tosyl-2-oxazolines,[5] only in the presence of TlOEt/EtOH in DME can 4-ethoxy-2-oxazolines,[5] important intermediates for α-hydroxy lactones, be obtained.

We now report that readily available BetMIC[6] (**3**) reacts with ketones and aldehydes to afford the same 4-ethoxy-2-oxazolines under mild conditions which avoid the use of thallium (KO^{t}Bu, EtOH, in THF at 0 °C, for 1-2 h). BetMIC is easily prepared[6] in two steps from benzotriazole **1**, formaldehyde, and formamide to give initially the Mannich product **2** (*cf* ref.7), which is then transformed to BetMIC with $POCl_3$.



1 **2** **3**

7 **6 a:** R' = OEt, **b:** R' = Bt **4** **5**

BetMIC combines two unique properties, the good leaving ability of benzotriazole [8] and a high acidity of the methylene protons.[9] Under conditions typically used to convert a carbonyl to a cyano group with TosMIC[3] (KO^tBu/EtOH in DME at 0 °C to room temperature, 2 -3 h), BetMIC reacted with cyclohexanone to give mainly 4-ethoxy-2-oxazolines **4** with only a small amount of the expected cyclohexylnitrile. Substituting THF for DME, gave complete conversion of ketones to oxazolines **4**; under these conditions, TosMIC gives 1-formylamino-1-tolylalkenes.[10] Table 1 shows the structures and the yields of the products obtained with BetMIC.

Table 1. The Preparation of 4-Ethoxy-2-oxazolines **4**

4	R^1	R^2	Yield(%)	Formula	MW(calcd)	MW(found)
a	$-(CH_2)_5-$		65[a]	-	-	-
b	CH_3	$(CH_2)_3CH_3$	93[b]	$C_{10}H_{19}NO_2$	185.1416	185.1407
c	CH_3	$(CH_2)_5CH_3$	92[b]	$C_{12}H_{23}NO_2$	213.1729	213.1731
d	$-(CH_2)_6-$		63[b]	$C_{11}H_{19}NO_2$	197.1416	197.1426
e	$-(CH_2)_4-$		59[b]	$C_9H_{15}NO_2$	169.1103	169.1105

a. B.p 95-97 °C/10 mm (lit.[5a] b.p 96-98 °C/10 mm Hg). b. The compound isolated was pure (≥ 97% by nmr) and directly used for hydrolysis.

The reaction seems to work best with alicyclic ketones. When benzophenone was used, only partial conversion to the oxazoline was achieved. Likewise, acetophenone afforded the desired product in only 15%, after distillation. Steric reasons can explain the reluctance of these ketones to undergo complete reaction. The conversion of **4** into synthetically useful α-hydroxyaldehydes **5**, was performed readily under conditions previously reported[5b] and the products were obtained in moderate yields. Table 2 lists examples of representative hydrolyses.

Table 2. The Conversion of 4-Ethoxy-2-oxazolines **4** into α-Hydroxyaldehydes **5**

5	R_1	R_2	Yield[a](%)	B.p(°C/mm Hg)	Formula	MW(calcd)	MW(found)
a	$-(CH_2)_5-$		35	70-73/5[b]	-	-	-
b	CH_3	$(CH_2)_3CH_3$	77	65-67/7.5	$C_7H_{14}O_2$	101.0966	101.0956[c]
c	CH_3	$(CH_2)_5CH_3$	51	68-70/2	$C_9H_{18}O_2$	129.1279	129.1264[c]

a. Isolated yield. b. Lit.[5a] b.p 80-82 °C/12 mm Hg. c. HR for $(M - CHO)^+$.

Under the conditions described above, arylaldehydes gave oxazoles **7**. Absence of EtOH does not affect the outcome of the reaction. Presumably 4-ethoxy- (**6a**) or 4-(benzotriazol-1-yl)-2-oxazoline (**6b**), respectively, are the intermediates under the respective conditions, which lose easily one mole of ethanol or benzotriazole, to give the same products **7**.

Table 3. The Preparation of 5-Substituted oxazoles **7**

7	R	Yield(%)	Purification[a]	mp(°C) or bp(°C/mm Hg)	Lit. mp(°C) or bp(°C/mm Hg)	Lit. Ref.
a	Ph-	69	A	37-38	40-42	11
b	p-F-C_6H_4-	68	B	37-39	[b]	-
c	p-CH_3O-C_6H_4-	63	B	67-69	70-71	11
d	2-furyl	35	C	92-94/2	61-63/0.3	12
e	3-pyridinyl	42	A	63-64	64-65	12

[a] A. Column chromatography. B. Sublimation. C. Distillation. [b] Anal. Calcd for C_9H_6FNO: C, 66.25; H, 3.70; N, 8.58. Found: C, 66.32; H, 3.65; N, 8.58.

All products were characterized by ^1H- and ^{13}C-NMR, and mass spectra, in addition to any existing information from the literature. Table 4 presents characteristic signals of the ^{13}C-NMR spectra of products **4** and **7**; the corresponding spectra for **5** are collected in Table 5.

Table 4. ^{13}C-NMR spectra ($CDCl_3$) of oxazolines **4** and oxazoles **7**

Comp.	C-2	C-4	C-5	4-Substituent	5-Substituent
4a	156.6	99.6	86.0	64.4, 15.0	35.5, 29.0, 24.9, 22.8, 22.5
4b	156.6	101.1	90.0	64.8, 15.2	39.2, 32.0, 29.2, 29.1, 22.6, 22.0
4c	156.9	98.9	95.2	64.3, 15.0	38.9, 30.4, 23.6, 23.5
4d	156.7	99.2	87.1	64.5, 15.0	39.3, 25.2, 22.7, 18.0, 13.6
	156.8	100.4	86.7	64.5, 13.8	32.6, 26.4, 23.7, 22.9, 13.7
4e	156.8	99.5	87.3	64.8, 15.2	39.9, 31.6, 29.6, 24.0, 22.6, 18.1, 14.1
	156.9	100.7	86.9	64.8, 15.0	33.2, 31.7, 29.9, 24.4, 23.3, 22.5, 14.1
7a	150.3	121.4	151.4	-	128.8, 128.5, 127.7, 124.3
7b	150.1	120.5	150.4	-	162.3 (249 Hz), 125.9 (8 Hz), 123.6, 115.6 (22 Hz)[a]
7c	149.8	119.8	151.4	-	159.8, 125.8, 114.2, 120.5, 55.2
7d	149.8	121.3	143.9	-	143.3, 142.9, 111.4, 107.5
7e	149.2	122.5	151.0	-	148.5, 145.5, 131.2, 123.7, 123.4

[a] Doublets (F-coupling) *J* values indicated in brackets.

In conclusion, BetMIC, easily prepared in multigram quantities from inexpensive starting materials, is a stable, non-hygroscopic solid, and its condensation under mild conditions with carbonyl compounds to form oxazoles, offers a possible and attractive alternative to TosMIC, which is expensive and moisture-sensitive. The use of BetMIC to convert ketones into α-hydroxyaldehydes avoids the use of toxic thallium.

Table 5. ^{13}C-NMR spectra ($CDCl_3$) of α-hydroxyaldehydes **5**

5	R^1	R^2	CHO	-C-OH
a	41.8, 31.3, 26.9, 24.9, 20.4		204.0	76.6
b	36.9	25.2, 22.9, 22.5, 13.8	204.0	77.9
c	37.2	31.5, 29.4, 22.9, 22.5, 22.4	204.0	77.8

Experimental

Preparation of BetMIC.- Benzotriazole **1** (47.65 g, 0.40 mole), paraformaldehyde (36.0 g, 1.20 mole) and formamide (75 mL, 2.22 mole) were mixed in toluene and the water was azeotropically distilled using a Dean-Stark trap for 5 h. A 27% aq. NaCl solution was then added (100 mL) and the mixture was kept at -5°C overnight. The crystalline precipitate 1-(formylaminomethyl)benzotriazole **2** was filtered and washed with water and ether, and then air dried (55.53 g, 79%, mp 140-141 °C; lit.[13] mp 146-147 °C). To a cold (0°C) suspension of **2** (52.8 g, 0.30 mole) in CH_2Cl_2 (300 mL) and triethylamine (300 mL, 2.16 mole), phosphorous oxychloride (27.6 mL, 0.30 mole) was added and the mixture stirred for 2 h. Ice (600 g) was then added, the organic layer separated and washed with ice-water. Concentration of the solution in rotary evaporator yielded a brown solid (40.1 g). After extraction with ether and removal of solvent, BetMIC was obtained as a golden yellow solid (28.8 g, 61%), mp 99-101 °C; lit.[13] mp 106-107 °C; ^{1}H-NMR ($CDCl_3$) δ 8.11(d, *J*= 7 Hz, 1H), 7.69-7.47(m, 3H), 6.22(s, 2H); ^{13}C-NMR ($CDCl_3$) δ 163.4(NC), 146.1, 131.7, 128.9, 125.0, 120.5, 108.8, 52.3.

*General Procedure for the Preparation of 5-Substituted-4-ethoxy-2-oxazoline **4** or 5-Substituted Oxazole **7**.*- To a cold (0 °C) solution of BetMIC (1 equiv.) in THF (5 mL), containing the the carbonyl compound (1 equiv.) and absolute ethanol (2 equiv.), solid potassium *t*-butoxide (2 equiv.) was added portionwise under N_2. A yellow precipitate (containing primarily benzotriazole, as shown by ^{1}H- and ^{13}C-NMR) was often observed. The mixture was stirred for 2 h in ice-bath and THF was then removed under reduced pressure. The product was isolated from the solid residue by ether extraction. Purification was carried out as reported in the Tables for the individual compounds.

*Hydrolysis of 4-ethoxy-2-oxazolines **4**. General Procedure.*- A mixture of 4-ethoxy-2-oxazoline (20 mmol), tetrahydrofuran (15 mL) and 5% hydrochloric acid (10 mL) was stirred at room temperature overnight. The solution was then diluted with water and extracted with diethyl ether (4 x 15 mL). The combined extracts were washed with 5% sodium hydrogen carbonate and dried over magnesium sulfate. Evaporation of the solvent gave crude product which was further purified as reported in the Tables for individual compound.

References

1. A. M. van Leusen, G. J. M. Boerma, R. B. Helmholdt, H. Siderius, J. Strating, *Tetrahedron Lett.*, **1972**, 2367.
2. O. H. Oldenziel, D. van Leusen, A. M. van Leusen, *J. Org. Chem.* **1977**, *42*, 3114.
3. O. H. Oldenziel, J. Wildeman, A. M. van Leusen, *Org. Synth.*, **1977**, *57*, 8.
4. A. M. van Leusen, B. E. Hoogenboom, H. Siderious, *Tetrahedron Lett.* **1972**, 2369.
5. (a) O. H. Oldenziel, A. M. van Leusen, *Tetrahedron Lett.* **1974**, 163. (b) *idem. ibid.* 167.
6. A. R. Katritzky, M. Sutharchanadevi, L. Urogdi, *J. Chem. Soc. Perkin Trans. 1*, in preparation.
7. A. R. Katritzky, M. Drewniak, *J. Chem. Soc. Perkin Trans. 1*, **1988**, 2339.
8. A. R. Katritzky, *Farmaco, Ed. Sci.*, **1988**, *43*, 1175; *C. A.* **1989**, *111*, 7245c.
9. D. Hoppe, *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 789.
10. U. Schöllkopf, R. Schröder, E. Blume, *Liebigs Ann. Chem.* **1972**, *766*, 130.
11. C. Tanaka, *Yakugaku Zasshi*, **1965**, *85*, 186; *C. A.* **1965**, *62*, 16222c.
12. H. Saikachi, T. Kitagawa, H. Sasaki, A. M. van Leusen, *Chem. Pharm. Bull.*, **1979**, 27, 793.
13. H. Saikachi, H. Sasaki, T. Kitagawa, *Chem. Pharm. Bull.*, **1983**, *31*, 723.

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