Synthesis of 1,2,4-Triazoles and 1,2,4-Oxadiazoles [1] Yang-i Lin*, Joseph J. Hlavka, Panayota Bitha and S. A. Lang, Jr.

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Monothiodiacylamines reacted regiosepecifically with hydrazines and hydroxylamine to give substituted 1,2,4-triazoles and 1,2,4-oxadiazoles in excellent yields.

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The condensation of diacylamines $\bf 1$ with hydrazines to yield substituted 1,2,4-triazoles $\bf 2$ and $\bf 3$ is described as the Einhorn-Brunner reaction [2,3]. The reaction as originally reported has two limitations. It is only regiospecific if $\bf R$ is sufficiently different from $\bf R'$; for example, $\bf R=\bf H$ and $\bf R'=\bf C_6\bf H_s$ [4], and it cannot be extended to a practical synthesis of substituted 1,2,4-oxadiazoles $\bf 5$ [5]. Recently, we reported an improved Einhorn-Brunner reaction for the synthesis of 1,2,4-triazoles $\bf 2$ and 1,2,4-oxadiazoles $\bf 5$ [6] in which the (dimethylamino)alkylidene moiety [6-8] was utilized as a masked acyl function.

The regiospecifity of the new synthetic reaction is attributed to an extremely fast and selective replacement of the dimethylamino moiety in acetic acid by either R''NH-NH₂ or NH₂OH, which is followed by a facile rate-determining intramolecular cyclization. However, this extension of the Einhorn-Brunner reaction has the limitation that R' derived from DMF dimethyl acetal or DMAC dimethyl acetal can only be H or Me. Therefore, another way of differentiating one of the C=O links in a diacylamine has been sought. We report here a regiospecific synthesis of substituted 1,2,4-triazoles 2 and 1,2,4-oxadiazoles 5 by the reaction of monothiodiacylamines 6 with hydrazines and hydroxylamine.

Results and Discussion.

Monothiodiacylamines 6 were prepared by reported methods [8,9]. The reaction of monothiodiacylamines 6 with either hydrazines or hydroxylamine in a 50/50 mixture of acetic acid and p-dioxane at 90° gave 1,2,4-triazoles 2 or 1,2,4-oxadiazoles 5, respectively, in excellent yields (80-97%). The condensation of the monothiodiacyl-

Table I
Substituted 1,2,4-Triazoles

Compound	R	R'	R"	Yield, %	Mp, °C	Formula
2a	3,5-(CH ₃ O) ₂ C ₆ H ₃	Н	Н	97	190-192 [a]	$C_{10}H_{11}N_3O_2$
2b	3,5-(CH ₃ O) ₂ C ₆ H ₃	H	CH ₃	80	97-99 [b]	$C_{11}H_{13}N_3O_2$
2c	3,5-(CH ₃ O) ₂ C ₆ H ₃	H	p-BrC ₆ H ₄	86	141-143 [c]	$C_{16}H_{14}NBrN_3O_2$
2d	3,5-(CH ₃ O) ₂ C ₆ H ₃	CH ₃	p-BrC ₆ H ₄	87	125-127 [d]	C ₁₇ H ₁₆ BrN ₃ O ₂
2 e	$p\text{-ClC}_6\text{H}_4$	CH ₃	C ₆ H ₅	80	90-93	$C_{15}H_{12}CIN_3$
2 f	$p\text{-ClC}_6\text{H}_4$	CH ₃	CF ₃ CH ₂	97	73-76	C ₁₁ H ₉ ClF ₃ N ₃
2g	p-CF ₃ C ₆ H ₄	C ₆ H ₅	Н	88	224-226	$C_{15}H_{10}F_{3}N_{3}$
2h	p-CF ₃ C ₆ H ₄	C_6H_5	CH ₃	84	115-117	$C_{16}H_{12}F_{3}N_{3}$
2i	p-CF ₃ C ₆ H ₄	C ₆ H ₅	C_6H_s	86	122-124	$C_{21}H_{14}F_3N_3$
2 j	p-CF ₃ C ₆ H ₄	C_6H_5	p -BrC $_6$ H $_4$	88	192-194	$C_{21}H_{13}BrF_3N_3$
2k	p-CF ₃ C ₆ H ₄	p-(CH ₃ O)C ₆ H ₄	C_6H_5	80	155-157	$C_{22}H_{16}F_{3}N_{3}O$
21	$p\text{-}\mathrm{CF_3C_6H_4}$	p-ClC ₆ H ₄	CF_3CH_2	90	166-168	$C_{17}H_{10}CIF_6N_3$
2m	p-ClC ₆ H₄	C_6H_5	C ₆ H ₅	93	141-143 [e]	$C_{20}H_{14}ClN_3$

Table II
Substituted 1,2,4-Oxadiazoles

Compound	R	R'	Yield, %	Mp, °C	Formula
5a	3,5-(CH ₃ O) ₂ C ₆ H ₃	Н	90	108-109 [a]	$C_{10}H_{10}N_2O_3$
5b	3,5-(CH ₃ O) ₂ C ₆ H ₃	CH ₃	93	90 - 91 [b]	$C_{11}H_{12}N_{2}O_{3}$
5e	$p\text{-ClC}_6\text{H}_4$	CH_3	96	92-94	C,H,CIN2O
5d	p-ClC ₆ H ₄	C_6H_5	94	122-124 [c]	C14H9CIN2O
5e	p-CF ₃ C ₆ H ₄	C_6H_5	94	100-102	$C_{15}H_9F_3N_2O$
5f	p-CF ₃ C ₆ H ₄	p-(CH ₃ O)C ₆ H ₄	91	125-127	$C_{16}H_{11}F_{3}N_{2}O_{2}$
5g	p-CF ₃ C ₆ H ₄	p-ClC ₆ H ₄	93	127-129	$C_{15}H_8ClF_3N_2O$

[a] Lit mp 108-109° [6]. [b] Lit mp 90-91° [6]. [c] Lit mp 124-125° [12].

Table III

Analytical Data of All New Compounds Reported

	С		Н		N		F		Cl or Br	
Compound	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2 e	66.8	66.7	4.49	4.50	15.6	15.8			13.1	12.8
2f	47.9	47.6	3.29	3.22	15.2	15.2	20.7	21.1	12.9	12.6
2g	62.3	62.2	3.48	3.42	14.5	14.5	19.7	19.7	_	_
2h	63.4	63.4	3.99	4.08	13.9	14.0	18.8	18.9	_	-
2 i	69.0	68.9	3.86	3.91	11.5	11.5	15.6	15.7		
2 j	56.8	56.6	2.95	2.90	9.46	9.23	12.8	12.8	18.0	17.9
2k	66.8	66.8	4.08	4.14	10.6	10.6	14.4	14.2	_	_
21	50.3	50.2	2.48	2.34	10.4	10.1	28.1	28.0	8.74	8.71
5 e	55.4	55.3	3.63	3.60	14.4	14.4	_	_	18.2	18.3
5e	62.1	62.1	3.12	3.21	9.65	9.56	19.6	19.8	_	
5f	60.0	60.0	3.46	3.45	8.75	8.70	17.8	17.4		
5g	55.5	55.2	2.48	2.35	8.63	8.50	17.6	17.6	10.9	10.9

amine 6 with hydrazines and hydroxylamine to the intermediates 7 and 8 occurred spontaneously at room temperature with evolution of hydrogen sulfide and disappearance of the yellow or orange color from the monothiodiacylamine 6. The cyclization of the intermediates 7 and 8 was effected at a higher temperature, for instance, 90°. Twenty 1,2,4-triazoles 2 and 1,2,4-oxadiazoles 5 have been synthesized and are tabulated in Table I and II.

The structures of 1,2,4-triazoles 2 and 1,2,4-oxadiazoles 5 synthesized in this report were all supported by nmr, ir, and elemental analysis data. The structures of 1,2,4-triazoles 2b and 2c have been previously determined by single-crystal x-ray analyses [6].

The overlap of the carbon 2p-orbitals and sulphur 3p-orbitals of the C=S group is less efficient than the 2p-2-overlap of the C=O link, owing to the different spatial symmetry of 2p- and 3p-orbitals. In addition, the interaction of the lone pair of the nitrogen with the C=S group results in a polarization towards a more stable singly-bonded form, e.g. C*-S-, the dipole being stabilized by delocalization of the positive charge within the remainder of the molecule. Therefore, a regiospecific reaction of monothiodiacylamines 6 with hydrazines or hydroxylamine is expected. The numerous reactions of thioamide and its derivatives with hydrazines and hydroxylamine reported in the literature [10] are supporting evidence for this reaction.

The present method provides a regiospecific synthesis of 3,5-diaryl-1,2,4-triazoles **2g-2m** and 3,5-diaryl-1,2,4-oxadiazoles **5d-5g** which are not available from the previous method [6]. Since every conceivable monothiodiacylamine can be prepared from the reported methods [8,9], the present method does provide a practical synthesis of 1,2,4-triazoles and 1,2,4-oxadiazoles.

EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus. Samples for elemental analyses were dried over phosphorus pentoxide under high vacuum for 1-24 hours. The nmr spectra were determined with a Varian Model HA-100 spectrometer; chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Monothiodiacylamines δ were synthesized by reported methods [8,9].

N-(Phenylthioxomethyl)-4-(trifluoromethyl)benzamide (6a) [9].

To a stirred solution of 62.6 g (0.30 mole) of p-trifluoromethylbenzoyl chloride in 250 ml of acetone was added a solution of 41.1 g (0.30 mole) of thiobenzamide and 23.7 g (0.30 mole) of pyridine in 250 ml of acetone. During the addition, the reaction mixture turned red and pyridine hydrochloride precipitated. After the addition was completed, the reaction mixture was heated to boiling for 15 minutes and then poured into 2000 ml of ice water to give 73.1 g of an orange product. Recrystallization from a chloroform/methanol mixture gave 28.4 g (31%) of $\bf 6a$ as orange crystals, mp 127-129°; nmr (deuteriochloroform): δ 7.2-8.5 (m, 9H), 10.03 (bs, 1H).

Anal. Calcd. for C₁₅H₁₀F₃NOS: C, 58.2; H, 3.26; F, 18.4; N, 4.53; S, 10.4. Found: C, 58.0; H, 3.22; F, 18.7; N, 4.09; S, 10.4.

1-(4-Bromophenyl)-3-phenyl-5-[4-(trifluoromethyl)phenyl]-1*H*-1,2,4-triazole (2j). Typical Procedure for **2a-m**.

A mixture of 3.09 g (0.010 mole) of N-(phenylthioxomethyl)-4-trifluoromethyl)benzamide (6a), 2.69 g (0.012 mole) of 4-bromophenylhydrazine hydrochloride, 0.984 g (0.012 mole) of sodium acetate, 15 ml of acetic acid and 15 ml of p-dioxane was stirred at 90° for 40 minutes. The volatile materials were removed under reduced pressure. The residue was triturated with water and then recrystallized from ethanol to give 3.91 g of 2j as tan crystals, mp 192-194°; nmr (deuteriochloroform): δ 7.1 ~ 7.8 (m, 11H), 8.15 (m, 2H).

3-Phenyl-5-(4-trifluoromethylphenyl)-1,2,4-oxadiazole (5e). Typical Procedure for 5a-g.

A mixture of 3.09 g (0.010 mole) of N-(phenylthioxomethyl)-4-trifluoromethyl)benzamide 6a, 0.834 g (0.012 mole) of hydroxylamine hydrochloride, 0.984 g (0.012 mole) of sodium acetate, 15 ml of acetic acid and 15 ml of p-dioxane was stirred at 90° for 40 minutes. After being cooled down to room temperature, the mixture was poured into 150 ml of water. The resulting mixture deposited 2.73 g (94%) of 5e as colorless crystals,

mp 100-102°; nmr (deuteriochloroform): δ 7.57 (m, 3H), 7.88 (d, J = 9 Hz, 2H), 8.25 (m, 2H), 8.40 (d, J = 9 Hz, 2H).

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REFERENCES AND NOTES

- [1] This is a continuation of our work published in reference [8]. After the completion of this work, the regiospecific reaction of monothiodiacylamines with hydrazines and hydroxylamine has been recently reported: L. L. Whitfield and E. P. Papadopoulos, J. Heterocyclic Chem., 18, 1197 (1981). Since our reactions were carried out under different conditions and a different set of 1,2,4-triazoles and 1,2,4-oxadiazoles was made with consistently high yields, we think it is worthwhile to publish our results.
- [2] A. Einhorn, E. Bischkopff and B. Szelinski, Ann. Chem., 343, 229 (1905).
 - [3] K. Brunner, Ber., 47, 2671 (1914).
 - [4] M. R. Atkinson and J. B. Polya, J. Chem. Soc., 3418 (1952).
- [5] The reaction of N-acetyl-p-methoxybenzamide with hydroxylamine in a mixture of acetic acid and p-dioxane at 110° for 1 to 5 hours gave a mixture of 5-p-methoxyphenyl-3-methyl-1,2,4-oxadiazole, N-acetyl-p-methoxybenzamide and p-methoxybenzamide; Y.-i Lin's unpublished work.
- [6] Y.-i Lin, S. A. Lang, Jr., M. F. Lovell and N. A. Perkinson, J. Org. Chem., 44, 4160 (1979).
 - [7] Y.-i Lin, and S. A. Lang, Jr., Synthesis, 119 (1980).
- [8] Y.-i Lin, T. L. Fields, V. J. Lee and S. A. Lang, Jr., J. Heterocyclic Chem., 19, 613 (1982).
- [9] J. Mirek and B. Nawalek, Rocz. Chem., 48, 243 (1974).
 [10] W. Walter and J. Voss, "The Chemistry of Amides", Interscience
- Publishers, Inc., New York, New York, 1970, Chapter VIII. [11] S. Cone, C. Corral and R. Madronero, Synthesis, 28 (1974).
- [12] T. Sasaki, Y. Suzuki and T. Yoshioka, Yuki Gosei Kagaku Kyokai Shi, 28, 742 (1970).