13rd International Electronic Conference on Synthetic Organic Chemistry (ECSOC-13), 1-30 November 2009.
http://www.mdpi.org/ecsoc-13/ & http://www.usc.es/congresos/ecsoc/13/

[c007]

Convenient synthesis of some novel amino acid coupled triazoles

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Abstract:

This study describes a promising one-pot synthesis of [2-(5-benzyl-4-phenyl-4H-[1,2,4]triazol-3-thio)-acetyl]-amino acid methyl esters **6a-h** and dipeptides **10a-e** were successfully synthesized starting from amino acid esters **5a-h, 9a-e** and azides **4**, **8a,b** respectively. On the other hand, azide **4** underwent Curtius rearrangement to the corresponding isocyanate which subsequently reacted with selected aliphatic and/or aniline derivatives to give the corresponding urea derivatives **11** and **12a, b**. Also reaction of isocyanate with secondary amines gave amide derivatives **13a, b**.

Keywords: triazoles, amino acids, azide coupling, peptides, Curtius.

Introduction

The emergence of drug resistance in diseases treatment calls for the availability of new chemotherapeutic agents able to overcome this problem. In the last few decades, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance.

For example, a large number of 1,2,4-triazole-containing ring system have been incorporated into a wide variety of therapeutically interesting drug candidates including Anti-septic, analgesic, anti-convulsant,[1-12] anti-biotic,[1] anti-allergic,[1] anti-inflammatory,[1-10, 13] diuretic,[1, 5, 8] fungicidal,[3, 10-13] insecticidal,[3, 10, 13] herbicidal,[3, 10,13] anti-bacterial,[3, 5, 6, 11, 12] anti-viral,[2, 3, 5, 7, 8, 10] anti-depressant,[2, 5, 9] anti-microbial,[2-5, 7, 10-12] anti-tumor,[3, 6, 9, 10] antihypertensive [5, 8, 9] and anti-migraine.[7]

Also, there are well known drugs containing the 1,2,4- triazole group e.g. anastrozole **I**, rizatriptan **II**, nefazodone **III**, vorozole **IV**, ribavirin **V**, fluconazole **VI**, letrozole **VII** and uniconazole **VIII** (Figure 1).

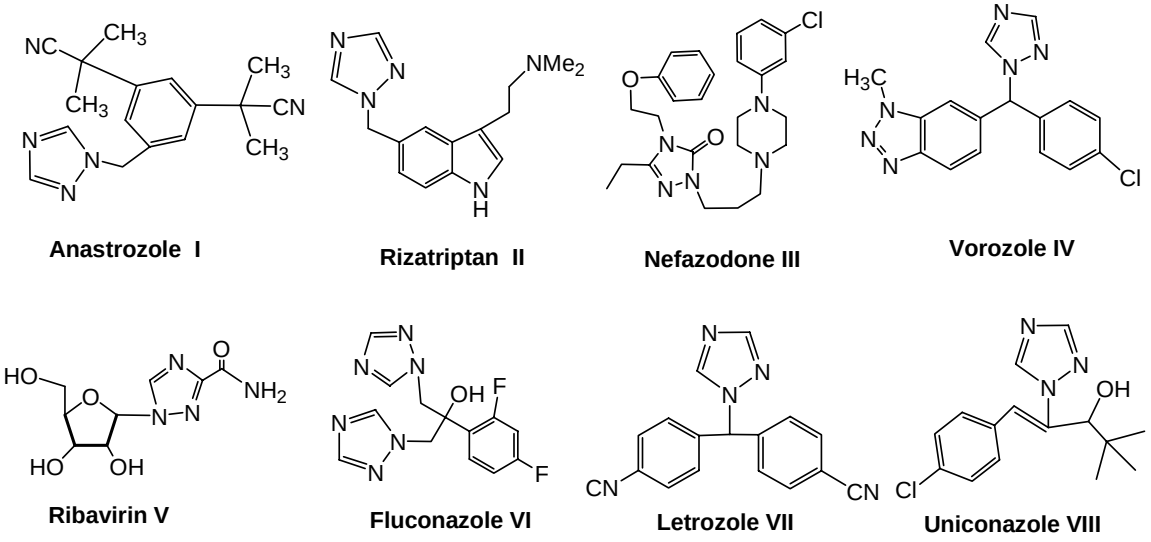


Figure 1. Biological active triazoles

On the other hand, many triazole derivatives have industrial applications, such as precursors for photosensitive materials (i.e., inks and toners),[14] polymer chemistry[11] and others.[15]

In this paper, we describe the development of a new series of 1,2,4-triazole derivatives, whose chemical modifications include coupled amino acid and dipeptide derivatives.

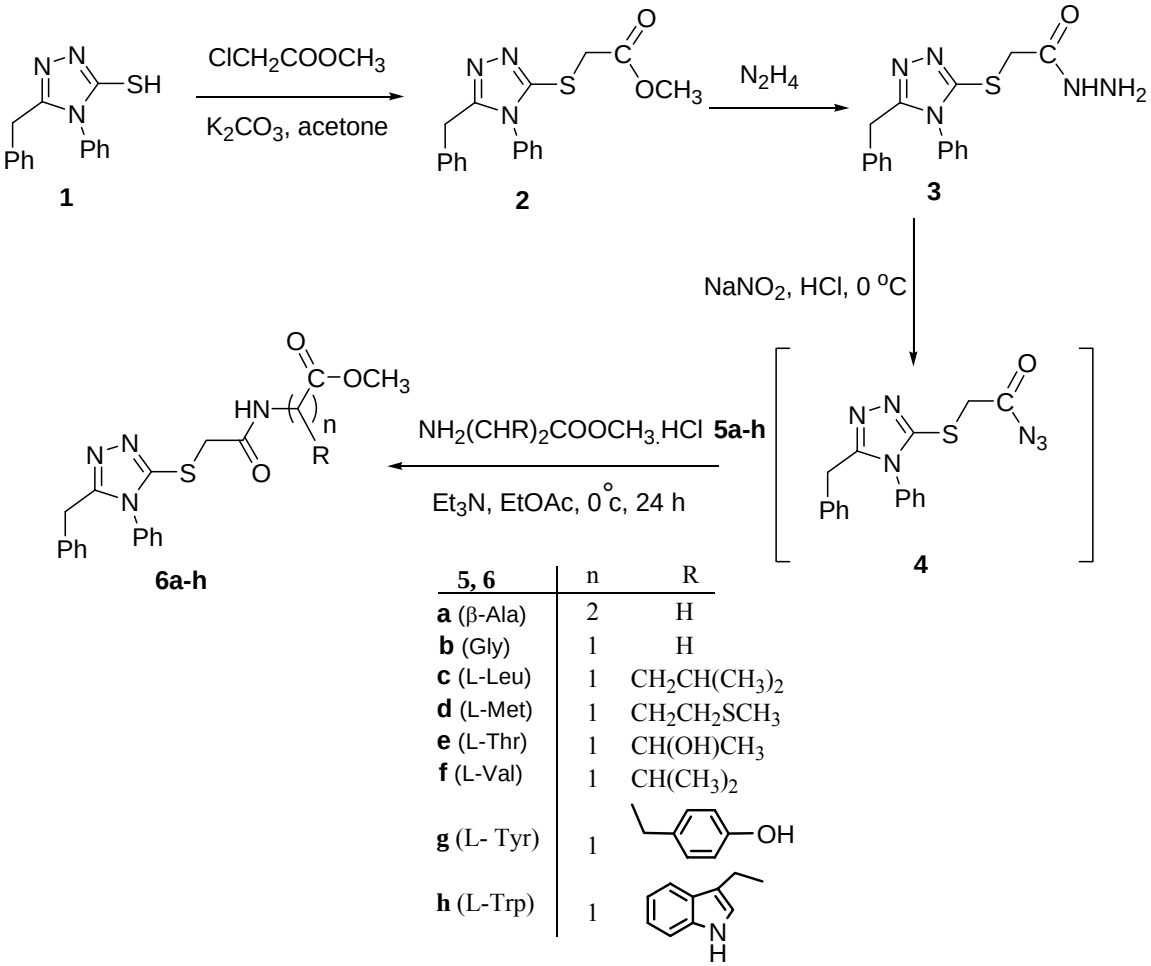
Results and Discussion

Synthesis of new amino acid derivatives coupled with biologically active heterocyclic moieties such as triazolo-quinazoline[16], quinoline[17], and pyradizinone[18] attracted our attention. In this work we studied 5-benzyl-4-phenyl-4H-[1,2,4]triazole-3-thiol (**1**) as biologically active heterocyclic precursor which was synthesized according to the established procedure.[2]

The hydrazide **3** could be prepared by regioselective *S*-alkylation[19] from **1** with ethyl chloroactetate to give the corresponding ester **2**, which was subsequently hydrazinolyzed by hydrazine hydrate.

The acyl azide pathway is one of the first method developed for peptide coupling by Curtius.[20] Synthesis of the target amino acid derivatives **6a-h** were successfully obtained *via* the azide coupling method[16-18, 21] which was reported to minimize the degree of racemization in amino acid coupling. The in situ generated azide **4** solution in ethyl acetate reacted with an amino acid methyl esters hydrochloride **5a-h** in the presence of triethyl

amine to afford [2-(5-benzyl-4-phenyl-4H-[1,2,4]triazol-3-thio)-acetyl]-amino acid methyl esters **6a**-h in good to moderate yield (Scheme 1).

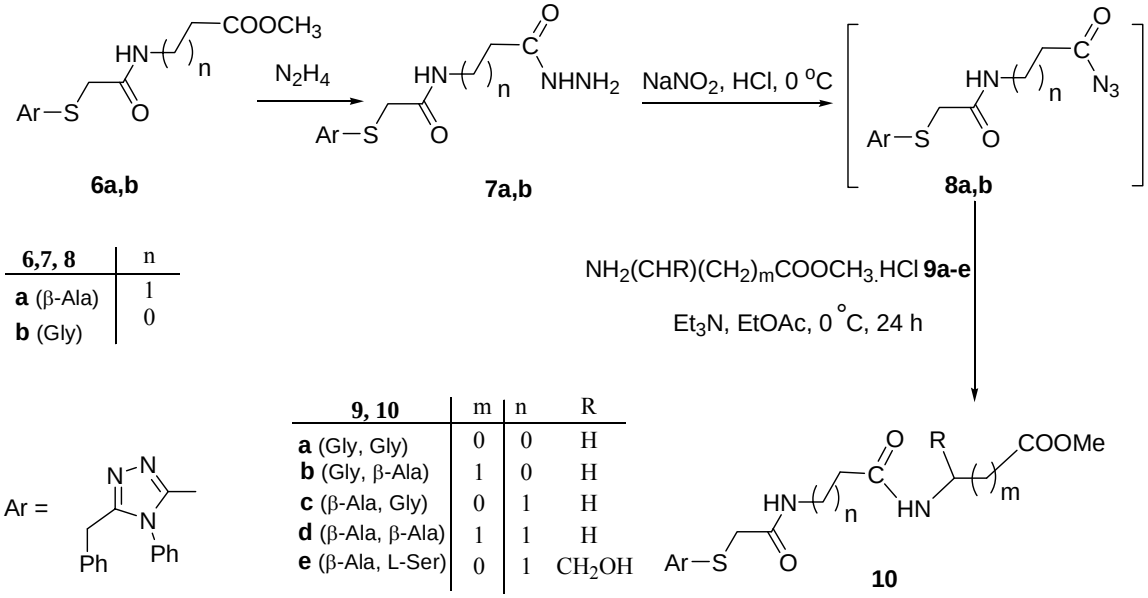


5, 6	n	R
a (β-Ala)	2	H
b (Gly)	1	H
c (L-Leu)	1	$CH_2CH(CH_3)_2$
d (L-Met)	1	$CH_2CH_2SCH_3$
e (L-Thr)	1	$CH(OH)CH_3$
f (L-Val)	1	$CH(CH_3)_2$
g (L- Tyr)	1	
h (L-Trp)	1	

Scheme 1

Further development of the azide coupling was obtained by the synthesis of *N*-substituted dipeptide derivatives **10a-e**. Thus, boiling the amino acid ester derivatives **6a, b** (β-Ala, Gly) with hydrazine hydrate gave the acyl hydrazides **7a, b** (Scheme 3).

Nitrosation of acyl hydrazides **7a, b** finally gave the acyl azides **8a, b** by treatment with $NaNO_2$ and HCl mixture. The *in situ* generated azides **8a, b** in ethyl acetate reacted with amino acid methyl esters hydrochloride **9a-e** in the presence of triethyl amine produced dipeptide derivatives **10a-e** in reasonable yield (Scheme 2).

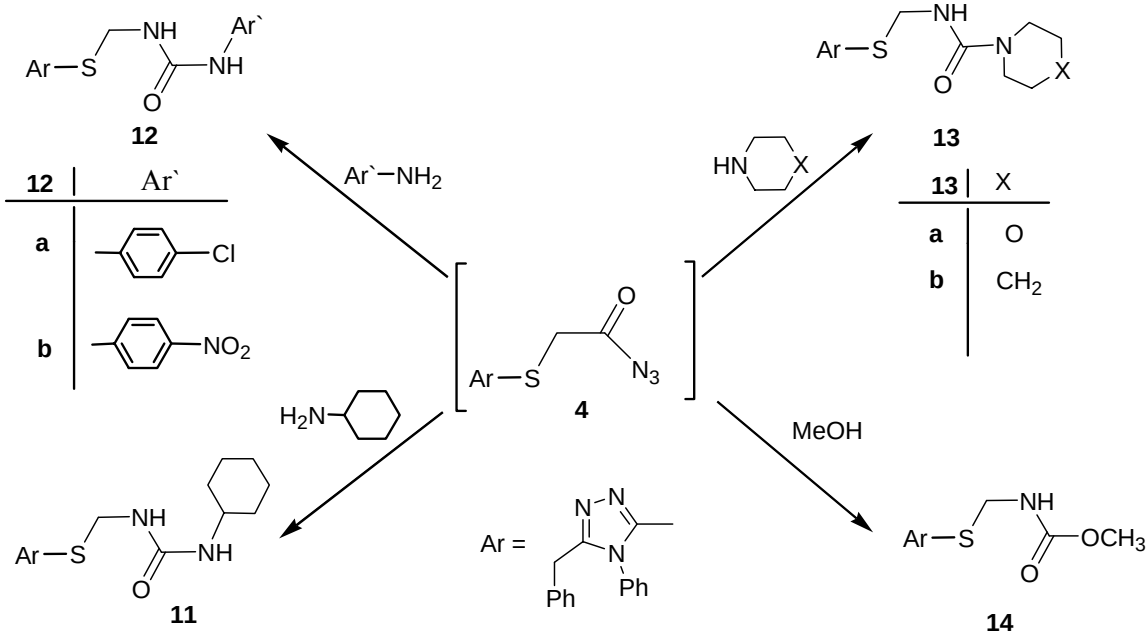


6,7, 8	n
a (β-Ala)	1
b (Gly)	0

9, 10	m	n	R
a (Gly, Gly)	0	0	H
b (Gly, β-Ala)	1	0	H
c (β-Ala, Gly)	0	1	H
d (β-Ala, β-Ala)	1	1	H
e (β-Ala, L-Ser)	0	1	CH_2OH

Scheme 2

An extension for this study was achieved by refluxing the azide **4** in non polar solvent such as benzene where Curtius rearrangement occurred and gave the corresponding isocyanate. On treatment in *situ* of isocyanate with selected aliphatic and/or aniline derivatives; urea derivatives **11** and **12a, b** were obtained. The reaction of isocyanate with secondary amines gave amide derivatives **13a, b** whereas with methanol gave carbamic acid derivative **14** (Scheme 3).



12	Ar`
a	Cl
b	NO_2

13	X
a	O
b	CH_2

Scheme 3

The structural assignment of ester **2**, acyl hydrazide **3,** *N*-substituted amino acid esters **6a-h**; acyl hydrazide **7a,b**, *N*-substituted dipeptides **10a-e**, urea derivatives **11** & **12a,b,** amide derivatives **13a,b** and carbamic acid derivative **14** is based on ^{1}H NMR, ^{13}C NMR, IR, spectral, mass and physicochemical analyses.

The ^{1}H NMR spectrum of the *N*-substituted dipeptide **10b** exhibits signals at δ 8.52, 6.61, 4.63, 3.73, 3.54-3.49 and 2.31 ppm corresponding to functionalities found at the dipeptide chain; two NH groups, CH_2 (glycyl residue), OMe of ester and two CH_2 (β-alanine residue) respectively, Figure 2.

The ^{1}H NMR spectrum of the urea derivative **12b** showed two characteristic signals at δ 10.11 and 5.64 ppm for two NH groups.

The ^{1}H NMR spectra for all compounds showed two characteristic signals one within the range δ 4.37-4.00 ppm for SCH_2 and the other within δ 412- 3.80 ppm for Ph$\underline{CH_2}$ Figure 2.

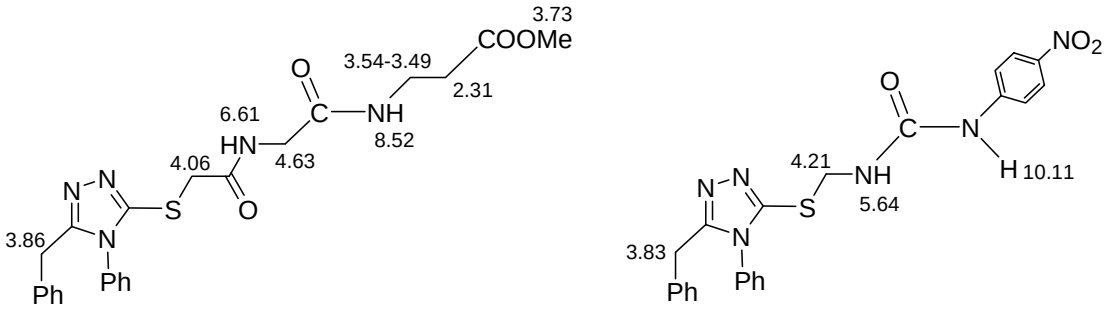


Figure 2. Selected ^{1}H NMR of compounds **10b** and **12b**

Experimental Section

General procedures. Solvent were purified and dried in the usual way. The boiling range of the petroleum ether used was 40-60 ^{o}C. Thin layer chromatography (TLC): silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption. Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. IR spectra measured with Perkin Elmer 1430 ratio recording. NMR spectra measured with Bruker (200 MHz and 300 MHz) and TMS (0.00 ppm) was used as internal standard. The mass spectra were measured with a KRATOS Analytical Kompact spectrometer.

The starting compound **1** was prepared according to described method.[2]

General procedure for azide method; preparation of 6a-h.

To a cold solution (-5 ^{o}C) of hydrazide **3** (0.34 g, 1.0 mmol) in acetic acid (6 mL), 1 N HCl (3 ml), and water (25 mL) was added a solution of $NaNO_2$ (0.87 g, 1.0 mmol) in cold water (3 mL). The reaction mixture was stirred at -5 ^{o}C for 15 min. The yellow syrup formed was extracted with cold ethyl acetate (30 mL), washed with cold 3% $NaHCO_3$, H_2O and finally dried (Na_2SO_4). To this solution amino acid esters **5a-h** (1.0 mmol) in ethyl acetate (20 mL) containing 0.2 mL of triethylamine was added. The reaction mixture was kept at -5 ^{o}C for 24 h., then at 25 ^{o}C for another 24 h. The solution was evaporated to dryness, and the residue was crystallized from petroleum ether/ ethyl acetate to give the desired product.

General procedure for preparation of hydrazides 7a,b.

To a solution of esters **6a,b (**1.0 mmol**)** in ethyl alcohol (30 mL), hydrazine hydrate (0.24 mL, 5.0 mmol) were added. The reaction mixture was refluxed for 4h, cooled; the precipitated white precipitate was filtered and crystallized from aq. EtOH.

General procedure for preparation of 10a-e

Dipeptides **10a-e** were prepared according to the previously described azide procedure.

General procedure for azide Curtius rearrangement to the corresponding isocyanate; preparation of 11-14

To a cold solution (-5 ^{o}C) of hydrazide **3** (0.34 g, 1.0 mmol) in acetic acid (6 mL), 1 N HCl (3 ml), and water (25 mL) was added a solution of $NaNO_2$ (0.87 g, 1.0 mmol) in cold water (3 mL). The reaction mixture was stirred at -5 ^{o}C for 15 min. The yellow syrup formed was extracted with cold benzene (30 mL), washed with cold 3% $NaHCO_3$, H_2O and finally dried (Na_2SO_4); the extract was filtered off and refluxed for 2 h. To this solution the appropriate amount of amine and/or MeOH (1.0 mmol) in benzene (20 mL) was added. The reflux was continued for an additional 2 h. The solvent was evaporated under reduced pressure and the residue was triturated with petroleum ether and crystallized from petroleum ether/ethyl acetate to give the desired product.

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