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Multi-gram scale mercury-free synthesis of optically pure 3,4,5-trisubstituted 1,2,4-triazoles using silver benzoate

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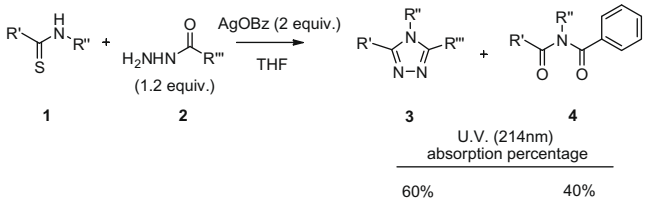
ABSTRACT

We report a new method using silver benzoate instead of mercury salts as a key reagent for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles. This method allows the introduction of a large variety of substituents in the three positions. We demonstrated that we could introduce one chiral center without any loss of the optical purity. This method is compatible with at least multi-gram scale-up.

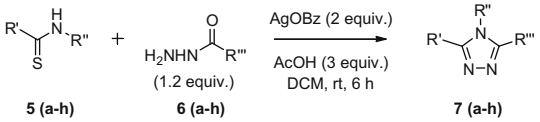
Triazoles are an important class of heterocyclic compounds. They are well-known for their antifungal,[1,2] antimicrobial,[3] antiviral,[4] anti-inflammatory,[5] anti-asthmatic,[6] antiproliferative,[7,8] and hypotonic activities.[9] 1,2,4-Triazoles were also used as amide bond isosteres for the design of receptor ligands in order to enhance their pharmacokinetic properties[10,11] or to mimic the *cis* configuration of the amide function observed in several peptides.[12] More recently, triazole-based agonists or antagonists targeting different receptors were described,[13,14] especially molecules based on the 3,4,5-trisubstituted 1,2,4-triazole scaffold.[15–18]

We previously reported the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles using mercury II diacetate as a key reagent during the ring formation.[19] However, this method has to be avoided for the synthesis of bioactive compounds, especially for batches dedicated to preclinical or clinical trials, because of the well-known toxicity of mercury derivatives. The replacement of mercury salts by a safer alternative was thus explored. We focused our work on the use of silver salts. A recent publication of Weibel et al.[20] extensively reviewed the use of silver in coupling and heterocyclization reactions. Silver salts are generally used for their halogeno-



Scheme 1. Synthesis of 1,2,4-triazole using silver benzoate and main side reaction.

Table 1
Coupling-cyclization step of thioamide **5a**–**h** with hydrazides



5 (a-h) **6 (a-h)** **7 (a-h)**

7	R′	R″	R‴	Yield (%)
a	Phenethyl	2,4-Dimethoxy benzyl	Benzyl[a]	49
b	Indolethyl	2,4-Dimethoxy benzyl	Benzyl[a]	47
c	Isopentyl	Benzyl	Benzyl[a]	90
d	2-Pyridyl	Benzyl	Benzyl[a]	70
e	3,4-Dichloro phenyl	2,4-Dimethoxy benzyl	Benzyl[a]	80
f	3,4-Dichloro phenyl	Benzyl	4-Methoxy benzyl[a]	66
g	Phenethyl	4-Methylbenzyl	Benzyl[a]	43
h	Phenethyl	3,4-Dichloro benzyl	Benzyl[a]	76

[a] Products obtained from commercial sources.

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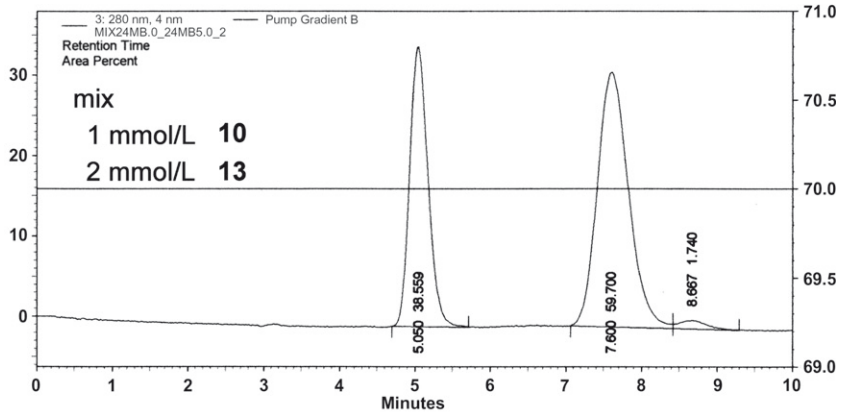
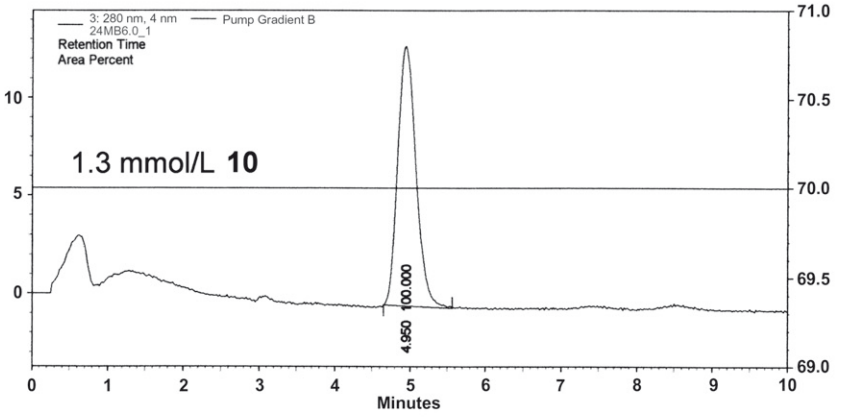
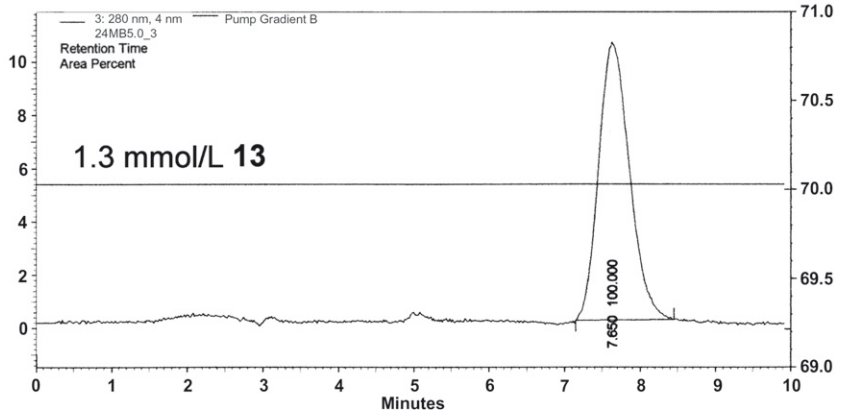
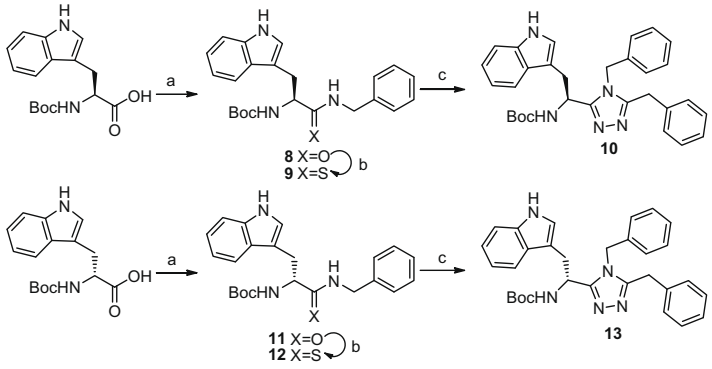


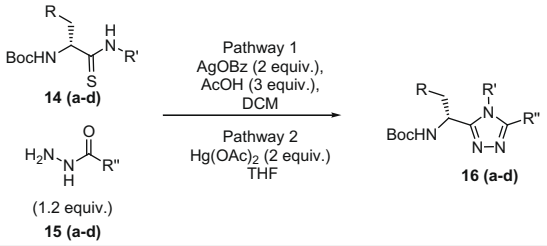






Scheme 2. Synthesis of triazoles **10** and **13**. Reagents and conditions: (a) DIEA, BOP (1 equiv), benzylamine (1.1 equiv), DCM, 30 min, rt; (b) Lawesson reagent (0.55 equiv), DME, 2 h, 80 °C; (c) phenylacetic hydrazide (1.2 equiv), AgOBz (2 equiv), AcOH (3 equiv), DCM, 6 h, rt. Chiral analysis parameters: column Chiracel OD, eluent system 70/30 hexane/isopropanol (v/v) 1‰ Et_2NH, monitoring at 280 nm.

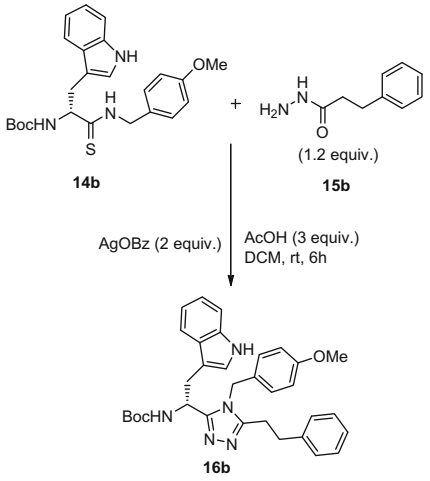
Table 2
Coupling-cyclization step of **16a–d**



16	R	R′	R″	Yield (pathway 1) (%)	Yield (pathway 2) (%)
a	Indol	4-Phenylbenzyl	Phenethyl	74	67
b	Indol	4-Methoxy benzyl	Phenethyl	73	65
c	Indol	2,4-Dimethoxy benzyl	Phenethyl	65	65
d	Indol	1-Naphthyl methyl	Phenethyl	87	64

All products were characterized by ^{1}H and ^{13}C NMR spectroscopy and LC/MS. No differences could be detected for the same compounds synthesized by both pathways.

Table 3
Multi-gram synthesis of triazole **16b**



Scale (mmol/g of thioamide **14b**)	Triazole **16b** (mmol/g)	Yield (%)
2.3 mmol/1.0 g	1.8 mmol/1.0 g	79
7.0 mmol/3.1 g	5.1 mmol/2.8 g	73
15.6 mmol/6.9 g	12.3 mmol/6.8 g	79
18.2 mmol/ 8.0 g	13.5 mmol/7.4 g	74

philicity and alkynophilicity whereas thiophilicity does not seem to be a much exploited property. Mercury salts are used for their thiophilicity properties more often than silver salts because of better specificity. We will demonstrate in this Letter that silver salts can be a very interesting alternative to mercury salts for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles.

Starting from thioamide and hydrazide[19,21] obtained using previously described synthetic methods, we ran a model reaction using various silver salts. Silver trifluoromethane sulfonate, silver(I) oxide, silver acetate, and silver benzoate were tested. Except for trifluoromethane sulfonate, all the salts led to the desired product in different levels of purity. The best results were obtained using silver benzoate. We decided to optimize the reaction conditions with this salt. The main problem we encountered was the formation of benzoylated amide **4** (Scheme 1), previously described by Avalos et al.[22]

After intensive optimization we found that running reaction in dichloromethane in mild acidic media (here 3 equiv of acetic acid) allowed us to obtain only triazole **3**.[23] An interesting fact is that the reaction time was reduced from three days to six hours just by changing thiophilic salt and reaction conditions, compared with the previous methodology using mercury II diacetate.

Exploration of the scope of the reaction led us to synthesize a small library of compounds with different substituents. Yields of the coupling–cyclization step are reported in Table 1.

Yields reported in Table 1 are from moderate to good and are irrespective of both the electron-withdrawing and electron-donating effects and to the nature of side chains (aromatic or alkyl groups).

We recently reported a new series of GHS-R1a ligands based on the triazole scaffold[24] and so obtained potent agonists and antagonists compounds. These antagonists are of great interest for the development of anti-obesity drugs. Our team is currently working on preclinical tests with some of these molecules. So we were interested in synthesizing such compounds using this new methodology. However, as the target compounds included a chiral carbon atom on the R′ position in their structure, we had to check that the whole process kept the molecule stereochemistry unchanged.

For this purpose, amides **8** and **11** were synthesized, starting from commercially available N-protected L and D tryptophan, respectively. After thionation reaction with the Lawesson reagent and purification, we obtained thioamides **9** and **12**. The coupling–cyclization reaction was carried out in the presence of silver benzoate to afford, respectively, triazoles **10** and **13**. Purification was performed on preparative reverse-phase HPLC. It was assumed that in this non-chiral purification environment enantiomers cannot be separated (Scheme 2).

After analysis by chiral HPLC we could conclude that our reaction pathway did not induce any epimerization on the carbon atom on R′ (in the limit of detection of the analytical method used).

To compare the synthesis using mercury II diacetate with the one using silver benzoate we synthesized a library of compounds by these two methodologies (Table 2).

Yields were clearly improved when using silver benzoate compared to mercury II diacetate.

As we are involved in the development of GHS-R1a ligands, large quantities of advanced intermediates bearing a chiral center-like triazoles **16** were necessary for intensive structure–activity relationship studies. Moreover, some compounds with interesting pharmacodynamic properties had to be resynthesized for further pre-clinical evaluations. With this new methodology in our hands, we were interested in performing the synthesis of several triazole derivatives in a multi-gram scale. Triazole **16b** was thus synthesized at different scales.[25] Yields are reported in Table 3.

Quantities could be increased up to 18 mmol of thioamide **14b** with no significant problem. This methodology using silver benzoate to achieve the coupling–cyclization step is robust enough to allow the synthesis of several grams of 3,4,5-trisubstituted 1,2,4-triazoles.

In conclusion, we report here a new method using silver benzoate as a key reagent for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles. This method allows the introduction of a large variety of substituents in the 3,4,5-positions, including chiral moieties in position 3, keeping the optical purity of the chiral center unchanged. This method is compatible with the synthesis of multi-gram batches of biological interesting compounds, due to the low toxicity of silver derivatives and the robustness of the reaction.

Supplementary data

Supplementary data (spectra, procedures and characterization data for products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.037.

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23. *General procedure for 1,2,4-triazole preparation:* Thioamide (1 equiv) and hydrazide (1.2 equiv) were diluted in the minimum of dichloromethane. Silver benzoate (2 equiv) was then added immediately followed by acetic acid (3 equiv). The mixture was stirred overnight at room temperature. Distillation of the solvent under reduced pressure gave a black oil, which was diluted in a solution of dichloromethane. A flash chromatography on silica gel, eluted with AcOEt/hexane 5/5 to MeOH 5% in AcOEt, afforded the pure triazole in 40–90% yield.
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25. NMR and mass characterization of compound **16b** ^{1}H NMR (DMSO-d_6, 300 MHz, 28 °C) δ (ppm) 1.25 (s, 9H, CH_3 Boc), 2.77–2.97 (m, 4H, CH_2–CH_2–phenyl), 3.27–3.44 (m, 2H, CH_2 β tryptophan), 3.70 (s, 3H, OCH_3), 5.05 (q, 1H, 8 Hz, CH α tryptophan), 5.18 (s, 2H, CH_2 *p*-methoxybenzyl), 6.76 (d, 2H, 9 Hz, H_3 and H_5 *p*-methoxybenzyl), 6.84 (d, 2H, 9 Hz, H_2 and H_6 *p*-methoxybenzyl), 6.92 (t, 1H, 8 Hz, H_5 tryptophan), 7.03–7.28 (m, 7H, H_2 and H_6 tryptophan, H_2 and H_3 H_4 H_5 and H_6 phenethyl), 7.34 (d, 2H, 8 Hz, H_4 and H_7 tryptophan), 7.73 (d, 1H, 8 Hz, NH Boc), 10.85 (s, 1H, NH tryptophan). ^{13}C{^{1}H} NMR (DMSO-d_6, 28 °C): δ (ppm) 25.9 (CH_2–CH_2–phenyl), 28.0 (CH_3 Boc), 28.3 (CH_2 β tryptophan), 31.7 (CH_2–CH_2–phenyl), 45.8 (CH_2–*p*-methoxyphenyl), 46.4 (CH α tryptophan), 55.1 (OCH_3), 78.6 (C quat Boc), 109.3 (C_3 tryptophan), 111.3 (C_7 tryptophan), 114.1 (C_3 and C_5 *p*-methoxybenzyl), 118.0 (C_4 tryptophan), 118.4 (C_5 tryptophan), 120.9 (C_6 tryptophan), 124.0 (C_2 tryptophan), 126.3 (C_4 phenethyl), 126.4 (C_1 *p*-methoxybenzyl), 127.0 (C_9 tryptophan), 127.7 (C_2 and C_6 *p*-methoxybenzyl), 128.2 (C_2 C_3 C_5 and C_6 phenethyl), 136.0 (C_8 tryptophan), 139.8 (C_1 phenethyl), 154.4 (CO Boc), 155.1 and 155.5 (C quat triazole), 158.8 (C_4 *p*-methoxybenzyl). MS (ES), *m*/*z*: 552.2 [M+H].