Synthesis of 3,4,5-Trisubstituted-1,2,4-triazoles

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1. Introduction

Triazoles are an important class of heterocyclic compounds not only as a core scaffold but also as a benzo-fused (triazolopyridines and triazolopyrazines are well-known examples) or functionalized one, such as alkylthiotriazoles. Indeed, the number of patents describing this attractive heterocycle (excluding benzo-fused compounds) with interesting biological properties is increasingly growing (Figure 1). Furthermore, among those patents, the 3,4,5-trisubstituted 1,2,4-triazole scaffold is clearly tending to become the most claimed.

It displays in fact a wide range of biological activities and can be used as amide bond isostere for the design of receptor ligands in order to enhance their pharmacokinetic properties.[1,2] Some pseudopeptide modifications (tetrazole,[3] for example) mimicking the cis amide bond orientation have been shown to introduce a very useful orientation of side chains. The biological activities of these pseudopeptides allowed considering that in some cases the active conformation of the peptide bond could be cis and not trans. 1,2,4-triazoles

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Mathieu Bibian was born in Millau (Aveyron), France, in 1984. He studied Chemistry at the University Montpellier II and received his M.Sc. degree in Biomolecular Chemistry in 2007. He is currently achieving his Ph.D. studies under the supervision of Dr. Jean-Alain Fehrentz. His research project is about the development and synthesis of new bioactive heterocyclic scaffolds.

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Anne-Laure Blayo was born in Pontivy, France, in 1983. She graduated as a Chemical Engineer in 2007 from the Ecole Nationale Supérieure de Chimie de Rennes, France. At the same time, she obtained her Master's degree in Molecular Chemistry from the University of Rennes, where she worked in Dr. R. Grée's group. Since 2007, she has been pursuing her Ph.D. degree under the direction of Dr. J.-A. Fehrentz. She is working on the synthesis of ghrelin receptor ligands based on the 1,2,4-triazole scaffold.

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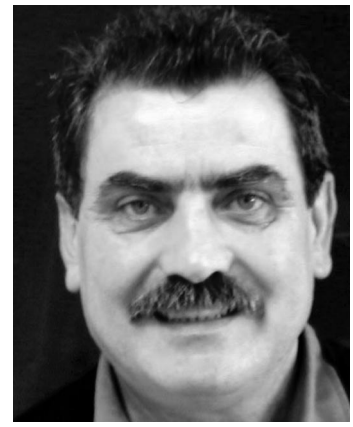
substituted in positions 3 and 4[4] have already been used as surrogates of the cis configuration of the amide function. The third substitution in 3,4,5-trisubstituted 1,2,4-triazoles enables an additional point of interaction between the potential ligand and its biological target.

The chemistry of 1,2,4-triazoles was previously reviewed[5−9] in papers covering both simple and fused as well as mono- or polysubstituted scaffolds. 1,2,4-Triazoles with specific substituents or substitution patterns, such as 5-amino-3-nitro-1,2,4-triazole and derivatives[10,11] or fluorinated triazoles,[12] as well as the chemistry of metal complexes of ligands containing 1,2,4-triazole residues[13] have also been the subject of review articles.

This present survey will entirely focus on the synthesis of monocyclic 3,4,5-trisubstituted 1,2,4-triazoles, excluding synthetic methods leading to fused triazoles, as well as those leading to alkylthiotriazoles. This intentional choice will allow us to go into detail and highlight synthetic pathways leading to this particular heterocycle, whose importance as a key scaffold for the design of compounds of biological interest was underlined above.

Several types of intermediates can be used to synthesize target compounds (Scheme 1): *N*-acylamidrazones, dichloroaldazines, and triazolopyrazines. *N*-acylamidrazones can particularly be obtained from a large variety of precursors,



Jean Martinez studied Chemistry at the National Graduate Chemistry School of Montpellier (France). After receiving his Ph.D. degree in 1972 he was awarded a permanent position at the CNRS. He completed his Thèse d'Etat in 1976 under the supervision of Professor F. Winternitz and performed postdoctoral studies with Professor E. Bricas in Orsay (France) and at Case Western University (Ohio, USA) with Professor M. Bodansky. Upon his return to France, he pursued research activities in the field of peptides and successively became Head of various research laboratories in Montpellier. In 1998, he was appointed Professor of the Faculty of Sciences and in 2001 Professor of the Faculty of Pharmacy in Montpellier. He is currently Head of the Institut des Biomolécules Max Mousseron and President of the European Peptide Society. His research interests are peptide chemistry and pharmacology, stereoselective synthesis of amino acids, chemistry on polymeric supports, mass spectrometry, artificial protein synthesis, computer-assisted peptide searching, and green chemistry.

Jean-Alain Fehrentz was born in Nancy, France, in 1955. He received his Ph.D. degree in Chemistry from the University of Nancy in 1983 and joined the Centre CNRS-INSERM de Pharmacologie Endocrinologie of Montpellier in the research group of Professor B. Castro. From 1989 to 1992 he was appointed as researcher at Sanofi Research in Montpellier. Then he moved to the Faculty of Pharmacy of Montpellier, working under the direction of Professor J. Martinez. His research interests focus on peptide aldehydes, enzyme inhibitors, peptidomimetics, and heterocycle-based receptor ligands.

depending on the nature of the substituents. In this paper, we will review these different methods.

2. Synthesis via N-Acylamidrazone Intermediates

The most common intermediates used to synthesize 3,4,5-trisubstituted 1,2,4-triazoles are *N*-acylamidrazones. Numerous precursors such as activated amide derivatives (chloromethylene amides, imidates, thioamides, thioimidates, and imidoylbenzotriazoles), amidrazones, *N*′-acetyl-*N*,*N*-dimethylhydrazonamides, oxadiazoles, *N*-nitrosoamidines, or arylphosphazoanilides can lead to *N*-acylamidrazones. More specific

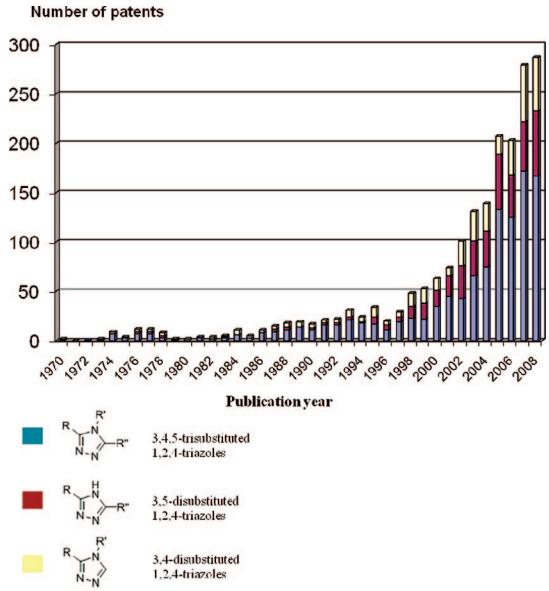
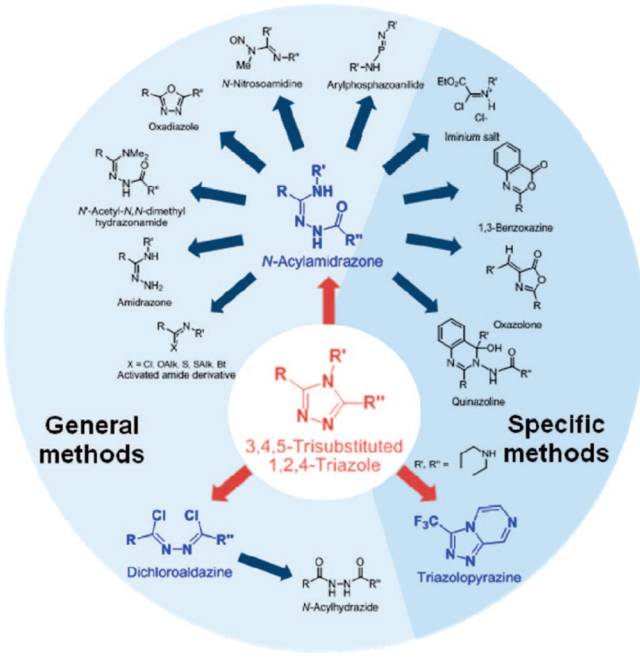


Figure 1. Evolution of the number of published patent applications claiming triazole compounds (excluding benzo-fused) with interesting biological properties. (Data obtained from Chemical Abstracts.)

Scheme 1. Different Synthetic Pathways Leading to 3,4,5-Trisubstituted 1,2,4-Triazoles



methods use iminium salts, 1,3-benzoxazines, oxazolones, or quinazolines as key precursors.

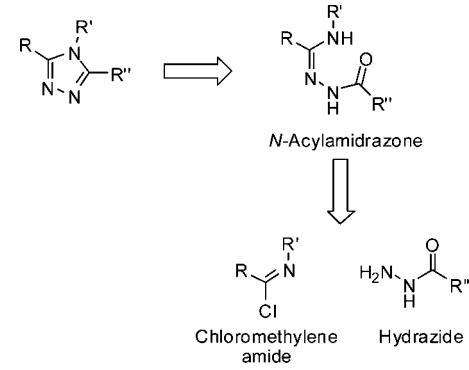
2.1. General Methods

2.1.1. Activated Amide Derivative Precursors

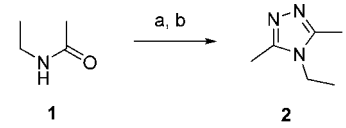
Among the general methods leading to *N*-acylamidrazones, the use of activated amide derivatives is one of the most exemplified in the literature. Although amides and hydrazides are intuitive precursors when analyzing the retrosynthetic scheme, amides generally need to be activated to condense properly with hydrazides.

2.1.1.1. Chloromethylene Amide Precursors. *N*-Acylamidrazones can be obtained by condensation of chloromethylene amides with hydrazides (Scheme 2). Several hydrazides are commercially available. For noncommercial ones, a widely used synthetic method is to react hydrazine with an ester precursor.[14−16] Different types of protected hydrazine have been used to access more complex *N*-protected hydrazides (especially phthalimide[17,18] and supported hydrazine[19]). The target hydrazides can be recovered by deprotection (or cleavage from the solid support in the case of solid supported reactions).

Scheme 2. Chloromethylene Amide and Hydrazide Precursors for the Synthesis of *N*-Acylamidrazones



Scheme 3. Atkinson and Polya Method[a]



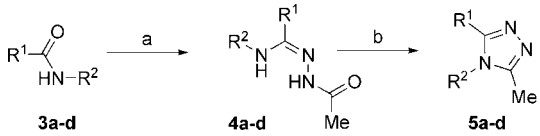
[a] Reagents and conditions: (a) $POCl_3$, $CHCl_3$, room temperature; (b) $CH_3CONHNH_2$, $CHCl_3$, reflux; isolated yield 23%.

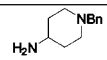
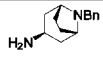
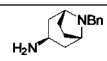
Concerning chloromethylene amides, they can easily be obtained by activation of amides with a chlorinating agent such as $POCl_3$.[20]

Atkinson and Polya[20] first described the preparation of triazole **2** starting from amide **1** and acetic acid hydrazide (Scheme 3). This method is easy to perform. However, yields are low due to the incomplete cyclization of the *N*-acylamidrazone intermediate.

The improvement of this methodology was investigated by Clemence[21] and Price.[22] First, Clemence prepared a series of compounds with a high degree of analgesic activity and poor anti-inflammatory activity via the condensation of chloromethylene amides (after chlorination of amides prepared from amines and acyl chlorides) and hydrazides (prepared from mixed anhydrides and hydrazine). The cyclization took place in refluxing toluene and yielded the triazole in moderate to good yields (40−88%). Later, Price and co-workers optimized the Atkinson and Polya's method with the aim of preparing triazoles **5a−d** substituted with piperidine or tropane groups in position 4 (Table 1). They were especially interested in this methodology consisting of a one-pot synthesis of the triazole scaffold. Thanks to their optimization work, it was demonstrated that conducting the chlorination step with phosphorus pentachloride gave the highest reproducibility and yields. Then refluxing in toluene with 5% molar *p*-toluene sulfonic acid led to better cyclization yields ranging from 50% to 65% depending on the substituents. The only used hydrazide precursor was acetic acid hydrazide, therefore leading to a methyl substituent in position 3 of the triazole ring. This optimized method made possible the synthesis of UK-427,857 (MARAVIROC),[23] a potent CCR5 receptor antagonist developed by Pfizer labo-

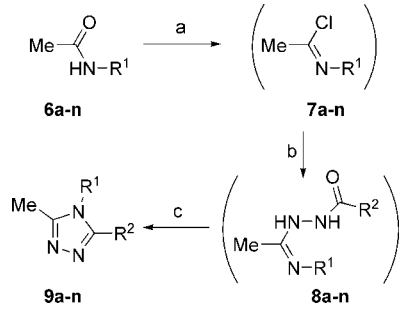
Table 1. Synthesis of Triazoles 5a−d[a]



5	R^1	R^2-NH_2	Yield (%) of 5
a	*i*-Propyl		50
b	*i*-Propyl		65
c	*i*-Propyl		61
d	*t*-Butyl		60

[a] Reaction conditions: (a) PCl_5, DCM, 0 °C then $CH_3CONHNH_2$, 1-pentanol, 0 °C to room temperature (b) *p*-TsOH, toluene, reflux.

Table 2. Synthesis of Triazoles 9a−n[a]



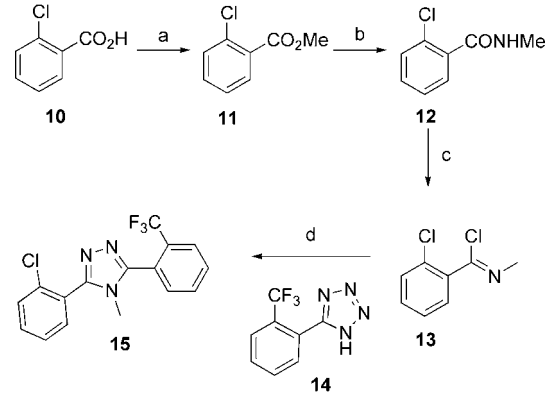
9	R^1	R^2	yield (%) of 9
a	methyl	phenyl	64
b	methyl	4-nitrophenyl	54
c	methyl	4-dimethylaminophenyl	56
d	*n*-butyl	phenyl	59
e	benzyl	phenyl	87
f	cyclohexyl	phenyl	65
g	4-methoxyphenyl	4-nitrophenyl	32
h	4-methoxyphenyl	4-dimethylaminophenyl	49
i	phenyl	phenyl	0
j	*tert*-butyl	phenyl	0
k	phenyl	4-nitrophenyl	0
l	4-nitrophenyl	4-nitrophenyl	0
m	methyl	4-pyridyl	50
n	methyl	3-pyridyl	27

[a] Reaction conditions: (a) Oxalyl chloride, 2,6-lutidine, CH_2Cl_2, 0 °C, 40 min; (b) $R^2CONHNH_2$, room temperature, 1−5 h; (c) aqueous $NaHCO_3$ solution (sat), reflux, 1−3 h.

ratories for the treatment of HIV infection, as well as the development of analogues of this compound.[24]

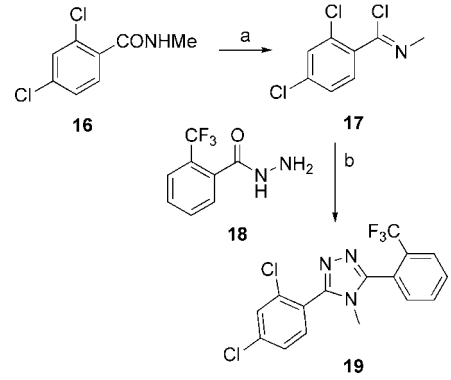
Lindström and co-workers[25] developed another method for the synthesis of 1,2,4-triazole derivatives using such intermediates. After treatment with oxalyl chloride, *N*-alkyl-substituted acetamides **6a−n** generally gave the corresponding triazoles **9a−n** in good yields using heteroaryl or aryl hydrazides (Table 2). In most cases, the triazoles could be isolated through recrystallization. No isolation was necessary for any intermediate, and the reaction could be performed in one flask by only changing the reaction solvent before the cyclization step. However when *N*-*tert*-butylacetamide

Scheme 4. Synthesis of Triazole 15[a]



[a] Reaction conditions: (a) $TMSCHN_2$, $MeOH/CH_2Cl_2$, 10 min; (b) 40% aq $MeNH_2$, 18 h; (c) $SOCl_2$, 70 °C, 4 h then room temperature 18 h; (d) toluene, 110 °C, 18 h.

Scheme 5. Synthesis of Triazole 19[a]



[a] Reaction conditions: (a) $POCl_3$, dioxane, 40 °C, 3 h; (b) 40 °C, 18 h then pH 6 (NaOH, 5 N), reflux, 20 h.

6j was used, no product was obtained. Gas evolution was observed when *N*-*tert*-butylacetamide was treated with oxalyl chloride, which indicated that the imidoyl chloride was formed, thus suggesting it was too sterically hindered to further react with the hydrazide. The reaction with *N*-arylacetamides is limited in scope: the electronic nature of the aryl substituents greatly influences the outcome of the reaction. An activating electron-donating group on the aryl ring seems to be necessary to allow reaction with oxalyl chloride, as postulated by Lindström et al. *N*-Phenyl- and *N*-4-nitrophenylacetamide failed to react with oxalyl chloride at 0 and 20 °C as witnessed by the lack of gas evolution.

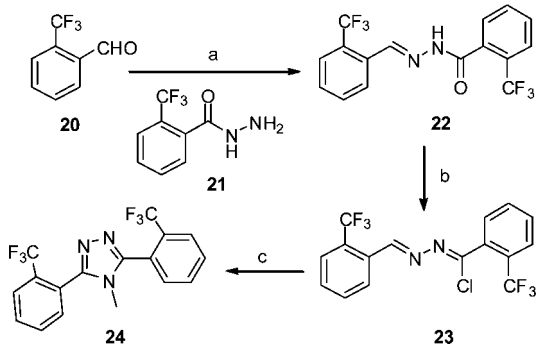
Aster and co-workers[26] used different synthetic approaches having in common a chloromethylene amide intermediate (Schemes 4−6). However, no yields were reported.

The mechanism of step d in Scheme 4 is supposed to involve the nucleophlic attack of the tetrazole ring on the imidoyl chloride followed by loss of nitrogen leading to triazole **15**.

2.1.1.2. Imidate Precursors. An alternative method is to replace the chloromethylene amide by an imidate, which also condenses with a hydrazide to give *N*-acylamidrazone (Scheme 7).

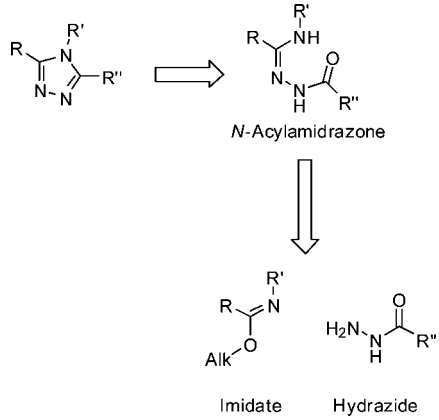
Adamantyl-substituted triazole **27**, identified as a potent and selective inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) by high-throughput screening,[27] was prepared in 80% yield by condensation of adamantyl-1-carbohydrazide to the imino ether of caprolactam **26**. Imino

Scheme 6. Synthesis of Triazole 24[a]

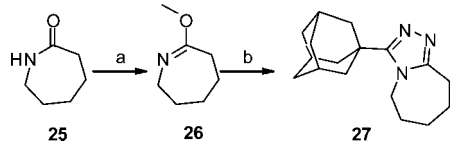


[a] Reaction conditions: (a) EtOH, reflux, 2 h; (b) $SOCl_2$, 75°C, 3 h; (c) 2 M $MeNH_2$/MeOH, 40% aq $MeNH_2$, 70°C, 1.5 h then room temperature 18 h.

Scheme 7. Imidate and Hydrazide Precursors for the Synthesis of *N*-Acylamidrazones



Scheme 8. Synthesis of Triazole 27[a]



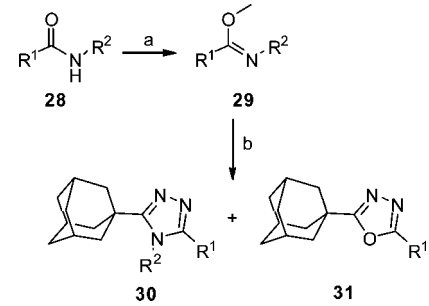
[a] Reaction conditions: (a) $Me_3O^+BF_4^-$, CH_2Cl_2; (b) adamantyl-1-carbohydrazide, toluene, reflux.

ether **26** was obtained from **25** by using Meerwein's salt (Scheme 8).

11β-HSD1 is an endoplasmic reticulum-associated enzyme that acts as an NADPH-dependent reductase and converts inactive cortisone into the active glucocorticoid cortisol. Thus, triazole **27** has been shown to have positive therapeutic effects in mouse models of obesity, diabetes, and atherosclerosis.

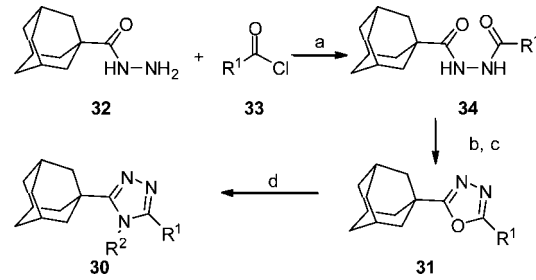
A first structure−activity relationship study was performed by varying the ring size of the starting cyclic amide, from a 5- to a 12-atom ring. Reducing the ring size from 7 atoms to 6 or 5 led to a significant drop-off in activity. On the contrary, increasing the ring size up to 12 atoms led to better inhibitors of the 11β-HSD1 with no selectivity vs β-HSD2. Substitution on the adamantyl fragment was also explored using a similar synthetic method as well as a series of acyclic analogues. For acyclic amides, methyl triflate was the reagent of choice for the formation of the methyl imino ethers, as also exemplified in several other series developed later by the same group of investigators.[26,28,29] Reaction of these imidates with adamantyl-1-carbohydrazide using the previously described conditions gave significant amounts of oxadiazoles **31** as unwanted byproducts (Scheme 9).

Scheme 9. Results Obtained with Methyl Triflate Reagent[a]



[a] Reaction conditions: (a) MeOTf, CH_2Cl_2; (b) adamantyl-1-carbohydrazide, toluene, reflux.

Scheme 10. Improved Synthesis of Triazoles 30[a]



[a] Reaction conditions: (a) Et_3N, CH_2Cl_2; (b) $SOCl_2$, pyridine; (c) toluene, reflux; (d) $R^2NH_3^+TFA^-$, 150 °C.

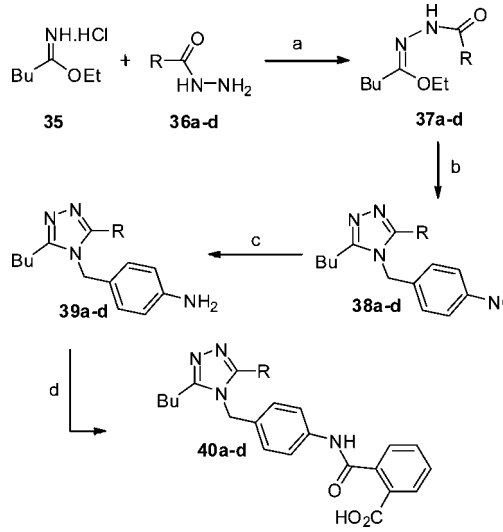
Improving the selectivity of this reaction proved to be difficult. However it was found that oxadiazoles **31** could be directly converted into triazoles **30** in the presence of amine excess.[30] To take advantage of this reaction, the authors redesigned the synthetic sequence. Adamantyl-1-carbohydrazide **32** was acylated with an acyl chloride **33** in the presence of triethylamine to give *N*-acylhydrazides **34**. These intermediates were converted into the imidoyl chlorides using thionyl chloride and further intramolecular nucleophilic attack of the oxygen doublet yielded oxadiazoles **31**. Finally, the oxadiazoles were heated in a sealed tube with the trifluoroacetate salt of a primary amine to provide the desired triazoles **30** (Scheme 10).

This method was further extended to the synthesis of 3-indole-4-methyl-5-phenyl-trisubstitued triazoles as inhibitors of β-HSD1.[26] More general approaches that enable obtaining *N*-acylamidrazones from oxadiazoles are presented in section 2.1.4 of the present review.

Another series of compounds from the same research group[31] based on bicyclo[2.2.2]octyltriazoles was also developed using the same imidate key intermediate as well as a series of compounds possessing a 1,2,4-triazolo[2,3-*a*]pyrrole structural subunit developed by Lawson et al. as α−4 integrin antagonists.[32]

An alternative pathway was described by Ashton et al. for the synthesis of potential angiotensin II antagonists (Table 3).[33] Imidate hydrochloride **35** was reacted with hydrazides **36a**−**d** to yield adducts **37a**−**d**. They were then converted into the triazoles **38a**−**d** upon heating in the presence of a primary amine. Although yields of the last step from compounds **39a**−**d** to compounds **40a**−**d** were indicated in this study, only one yield for the cyclization step of **37d** to **38d** was given.

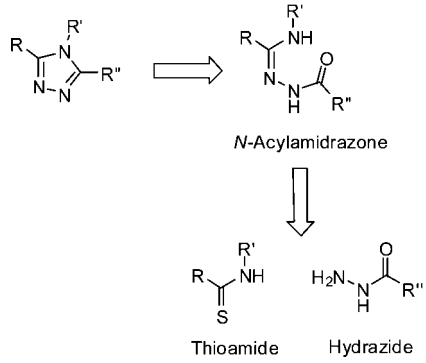
Table 3. Synthesis of Triazoles 40a−d[a]



40	R	yield[b] (%) of **38**	yield[c] (%) of **40**
a	phenyl	N.I.	64
b	4-pyridyl	N.I.	63
c	3-pyridyl	N.I.	54
d	2-furyl	61	85

[a] Reaction conditions: (a) EtOH, −10 to 5°C; (b) 4-nitrobenzylamine, EtOH, 45−70°C; (c) $SnCl_2 \cdot 2H_2O$, concentrated HCl, THF; (d) phthalic anhydride, THF. [b] Yields of isolated products for the synthesis of **38** from **37**. [c] Yields of isolated products for the synthesis of **40** from **39**. N.I.: not indicated.

Scheme 11. Thioamide and Hydrazide Precursors for the Synthesis of *N*-Acylamidrazones

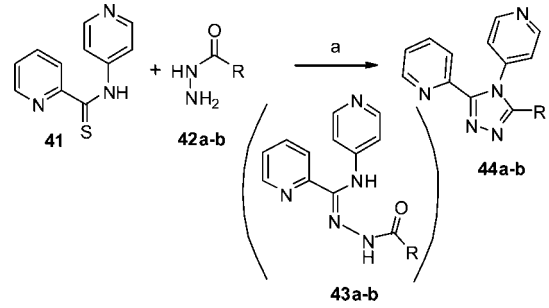


2.1.1.3. Thioamide Precursors. Another alternative for the synthesis of *N*-acylamidrazones is to condense thioamides and hydrazides (Scheme 11). Thioamides are easily available precursors and can be prepared either by employing a thioacylating method using thioacylbenzimidazolinones,[34,35] thionoacid derivatives of nitrobenzotriazoles,[36] or thioacyl-*N*-phthalimides,[37] by coupling reaction of arylmagnesium reagents with isothiocyanates,[38] or by reacting a thionating reagent on the corresponding amide. Known thionating reagents are P_2S_5,[39,40] R_3OBF_4/NaSH,[41] the Lawesson's reagent[42] and its fluorous[43] or supported[44] analogues, P_4S_{10}/Al_2O_3,[45] or thiourea.[46]

Klingele and Brooker[47] described the preparation of 1,2,4-triazoles **44a**,**b** via the condensation of thioamide **41** and hydrazides **42a**,**b**. The obtained acylamidrazones **43a**,**b** were cyclized by heating in refluxing *n*-butanol (116−118 °C) (Table 4).

Boeglin et al.[48] generalized a synthetic method (Table 5) developed by Hitotsuyanagi et al.[4] by demonstrating that a third point of diversity can be introduced by replacing formic hydrazide with substituted hydrazides. Starting from various thioamides **46a−h**, the cyclization step was performed at room temperature in the presence of various hydrazides and a thiophilic salt, such as mercury(II) acetate. The exploration of the scope of the reaction was performed starting from optically pure α-amino acids **45a−h**, and the optical purity of the final products **47a−h** showed an ee larger than 98%, indicating that the configuration of the starting α-amino acid was not affected during the process. To our knowledge, this method is the only one evidencing the possibility to introduce a chiral carbon atom in α of the position 3 of a 3,4,5-trisubstituted 1,2,4-triazole ring, keeping the optical purity of the chiral center. This methodology was widely used in our group for the synthesis of a new series of optically active ghrelin receptor ligands, starting from various hydrazides and thioamides.[49−52] Wu et al.[53] demonstrated that this method is applicable to microwave technology, but they only used

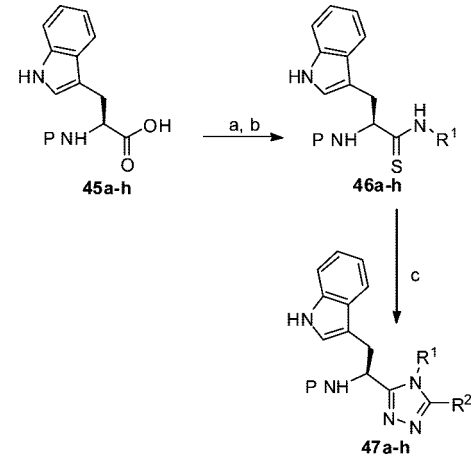
Table 4. Synthesis of Triazoles 44a–b[a]



44	R	yield (%) of **44**
a	phenyl	78
b	2-pyridyl	69

[a] Reaction conditions: (a) *n*-BuOH, reflux.

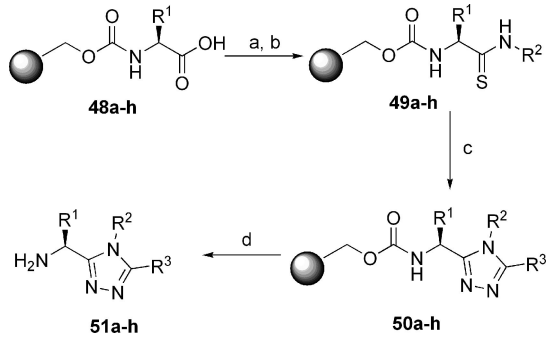
Table 5. Synthesis of Triazoles 47a−h[a]



47	P	R^1	R^2	yield (%) of **47**
a	Boc	2,2-diphenylethyl	benzyl	64
b	Z	*n*-hexyl	phenyl	47
c	Fmoc	*n*-hexyl	4-*N*-Boc-piperidinyl	31
d	Boc	$CH(CH_3)COO$*tert*-Bu	benzyl	80
e	Boc	methyl	indol-3-ylmethyl	50
f	Boc	methyl	indol-3-ylethyl	51
g	Boc	4-methoxybenzyl	indol-3-ylmethyl	49
h	Boc	2,4-dimethoxybenzyl	indol-3-ylmethyl	55

[a] Reaction conditions: (a) Coupling reaction with R^1NH_2; (b) Lawesson's reagent; (c) $R^2CONHNH_2$, $Hg(OAc)_2$, room temperature, 2−3 days.

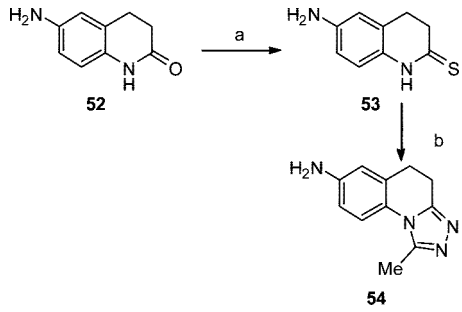
Table 6. Synthesis of Triazoles 51a−h[a]



51	R^1	R^2	R^3	purity[b] (%) of 51
a	benzyl	benzyl	benzyl	95
b	benzyl	indol-3-ylethyl	benzyl	81
c	benzyl	$CH_2-CH(Ph)_2$	benzyl	87
d	indol-3-ylmethyl	benzyl	benzyl	83
e	indol-3-ylmethyl	$CH_2-CH(Ph)_2$	benzyl	88
f	*i*-butyl	benzyl	benzyl	87
g	*i*-butyl	indol-3-ylethyl	benzyl	73
h	*i*-butyl	indol-3-ylethyl	phenyl	45

[a] Reaction conditions: (a) Coupling reaction with R^2-NH_2; (b) Lawesson's reagent, THF, reflux; (c) $R^3CONHNH_2$, $Hg(OAc)_2$, DMF, room temperature, 3 days; (d) TFA/DCM/H_2O/TIS (triisopropylsilane). [b] Purity was checked by LC/MS at 214 nm.

Scheme 12. Synthesis of Triazole 54[a]



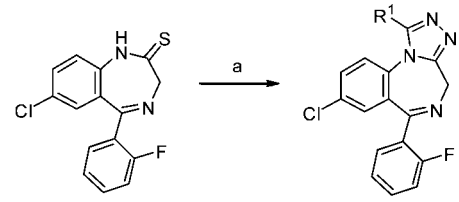
[a] Reaction conditions: (a) P_2S_5, Et_3N, CH_3CN, 70% yield. (b) $MeCONHNH_2$, cyclohexanol, reflux, 4h, 55% yield.

unasymmetric precursors. Apart from the fact that the reaction time is significantly reduced, there was no other significant improvement in the reaction by using microwave technology.

In a second set of experiments, Boeglin undertook the polymer-supported extension of this method (Table 6). An inverse anchoring of α-amino esters on their *N*-terminal function was achieved on a Wang resin through its *p*-nitrophenyl carbonate derivative[54] to yield *N*-urethane-linked α-amino esters. After saponification of the ester,[55] amines were coupled to the corresponding carboxylic acids **48a−h**. Conversion of the amide functions into thioamides **49a−h** was performed on support with Lawesson's reagent,[56] and direct conversion of thioamides to trisubstituted triazoles **50a−h** was achieved on support using benzoic or phenylacetic acid hydrazide in the presence of $Hg(OAc)_2$ at room temperature. After 3 days and classical washings, resins were submitted to cleavage conditions to yield triazoles **51a−h** in good to excellent purities.

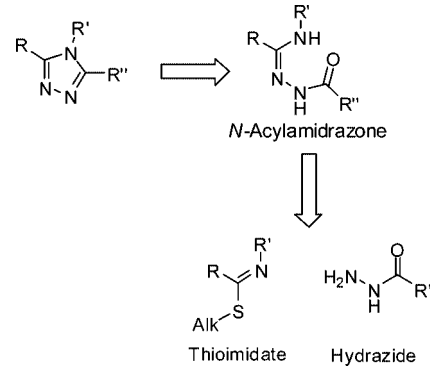
Zhang and co-workers[57] also used the thioamide precursor **53** for the synthesis of the tricyclic compound **54** (Scheme 12). This tricyclic scaffold allowed the development of a series of inotropic agents potentially useful in the treatment of congestive heart failure.

Scheme 13. Synthesis of Compounds 56[a]



[a] Reaction conditions: (a) $R^1CONHNH_2$, *n*-BuOH, AcOH, reflux.

Scheme 14. Thioimidate and Hydrazide Precursors for the Synthesis of *N*-Acylamidrazones



Other tricyclic scaffolds, triazolo[4,3-*a*][1,4]benzodiazepines **56**, were also synthesized following the same strategy in 68−80% yields (Scheme 13).[58] These compounds were tested as anticonvulsants.

Clemence[21] and Duplantier[21,59] reported a closely related strategy for the synthesis of 1,2,4-triazole. Thioamides and hydrazine were condensed and then acylated with acyl chlorides to form nonisolated acylamidrazones which were dehydrated to give triazoles. This methodology will be extensively reviewed in section 2.1.2.

2.1.1.4. Thioimidate Precursors. Thioimidates are also reported as *N*-acylamidrazone precursors. They are generally obtained via S-alkylation of thioamides (Scheme 14).

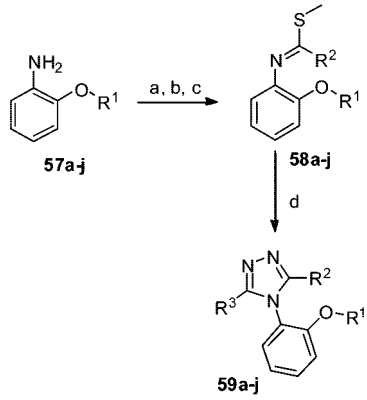
Kakefuda et al.[60] proposed performing the synthesis via intermediates **58a−j** (Table 7), obtained by thioamide S-alkylation achieved at 50 °C in acetonitrile. The condensation of the obtained thioimidates **58a−j** with a hydrazide at 120 °C in DMF yielded the trisubstituted triazoles **59a−j**. These compounds were found to be selective human vasopressin V_{1A} receptor antagonists.[61]

Klingele et al.[47] also proposed performing the synthesis via thioimidate intermediates **61a−f** (Table 8). After condensation of these compounds with a hydrazide in refluxing *n*-butanol, trisubstituted triazoles **62a−f** were obtained.

Di Marco[62] proposed an original method for the synthesis of fused [5,5]-1,2,4-triazoles **65a−i** via a tandem cyclopropane rearrangement−cyclization sequence. The methyl iodide-mediated rearrangement of thioamides **63a−i** proceeded in acetone at 60 °C to afford the HI salt of thioimidates **64a−i** in quantitative yields. The reaction of **64a−i** with a hydrazide allowed the formation of fused triazole rings **65a−i** (Table 9).

Thioimidates were also used by Duplantier et al.[59] as key precursors for the synthesis of human eosinophil phosphodiesterase inhibitors. Indeed, it is interesting to note here that Duplantier et al. used two different strategies to access to the triazole moiety: condensation of thioimidate and hydrazide in refluxing pyridine and condensation of thioamide

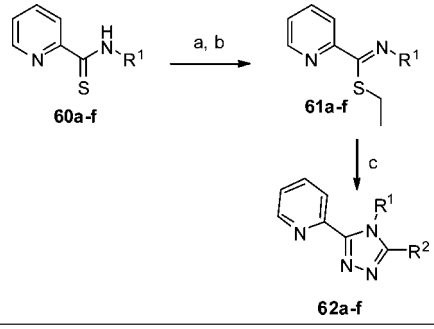
Table 7. Synthesis of Triazoles 59a−j[a]



59	R^1	R^2	R^3	yield (%) of **59**
a	methyl	methyl	3-phenylphenyl	70
b	methyl	methyl	2-phenylphenyl	17
c	methyl	methyl	4-phenoxyphenyl	72
d	methyl	methyl	4-benzyloxyphenyl	64
e	methyl	methyl	4-(pyrrol-1-yl)phenyl	65
f	methyl	methyl	4-piperidinophenyl	42
g	methyl	methyl	4-morpholinophenyl	31
h	methyl	ethyl	4-phenylphenyl	59
i	methyl	*n*-propyl	4-phenylphenyl	21
j	benzyl	methyl	4-phenylphenyl	66

[a] Reaction conditions: (a) R^2COCl, pyridine; (b) P_2S_5, toluene, 70 °C; (c) MeI, K_2CO_3, CH_3CN, 50 °C; (d) $R^3CONHNH_2$, DMF, 120 °C.

Table 8. Synthesis of Triazoles 62a−f[a]



62	R^1	R^2	yield (%) of **62**
a	4-methylphenyl	phenyl	52
b	4-methylphenyl	2-pyridyl	50
c	methyl	phenyl	59
d	methyl	2-pyridyl	52
e	*i*-butyl	phenyl	67
f	*i*-butyl	2-pyridyl	73

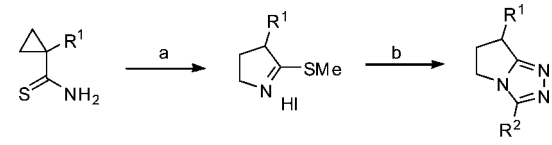
[a] Reaction conditions: (a) NaOEt, EtOH, room temperature; (b) EtBr, EtOH, 50 °C; (c) $R^2CONHNH_2$, *n*-BuOH, reflux.

and hydrazine followed by acylation (section 2.1.1.3). Unfortunately, no comparison of the two methods was reported by the authors. Yields were moderate to excellent for both strategies, depending on the examples.

2.1.1.5. Imidoylbenzotriazole Precursors. Alternative intermediates are imidoylbenzotriazoles (Scheme 15). They can be prepared from the reaction of secondary amides, oxalyl chloride, and benzotriazole in the presence of pyridine.[63]

Reacting imidoylbenzotriazoles **66a−d** with hydrazides in the presence of a catalytic amount of acetic acid under microwave conditions (Table 10) allowed Katritzky et al.[64] to obtain 1,2,4-triazoles **67a−d** via a simple intramolecular

Table 9. Synthesis of Triazoles 65a−i[a]



65	R^1	R^2	yield (%) of **65**
a	phenyl	phenyl	97
b	phenyl	methyl	97
c	phenyl	2-pyridyl	97
d	phenyl	3-pyridyl	87
e	phenyl	trifluoromethyl	52
f	phenyl	4-methoxyphenyl	97
g	phenyl	4-nitrophenyl	92
h	phenyl	*tert*-butyl	97
i	4-methoxyphenyl	phenyl	58

[a] Reaction conditions: (a) MeI, acetone, 60 °C; (b) $R^2CONHNH_2$, *i*-PrOH, TEA, 150 °C, 7−24 h.

Scheme 15. Imidoylbenzotriazole and Hydrazide Precursors for the Synthesis of *N*-Acylamidrazones

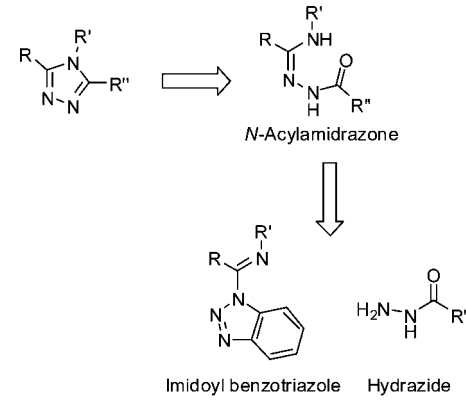
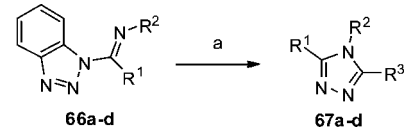


Table 10. Synthesis of Triazoles 67a−d[a]



67	R^1	R^2	R^3	conditions (*T* (°C), power (W), time (min))	yield (%) of **67**
a	benzyl	*p*-tolyl	methyl	80, 120, 10	77
b	methyl	*p*-tolyl	*p*-tolyl	80, 120, 5	94
c	*p*-tolyl	4-methoxyphenyl	*p*-tolyl	80, 120, 5	100
d	*p*-tolyl	4-methoxyphenyl	phenyl	80, 120, 10	88

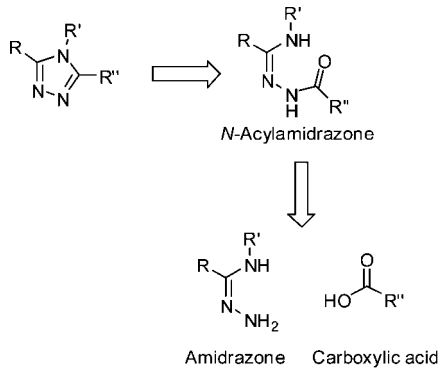
[a] Reaction conditions: (a) $R^3CONHNH_2$, AcOH, μw.

condensation followed by the loss of one molecule of water. Compounds were obtained in 77−100% yields.

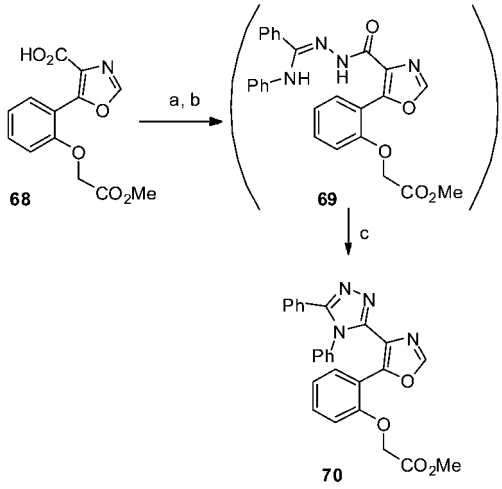
2.1.2. Amidrazone Precursors

N-Acylamidrazones can be obtained from condensation of carboxylic acids and amidrazones (Scheme 16). Amidrazones are readily available intermediates, and reaction of nitriles with hydrazine is frequently used for their preparation.[65] Alternative methods consist of reacting hydrazine with imidates or their salts,[66] imidoyl halides,[67] amides in the presence of $POCl_3$,[68] thioamides,[69] imidoylbenzotriazoles,[64] or ketenimines.[70] Further routes to amidrazones include reaction of amines with hydrazonoyl halides[71] or reduction of nitrazones by ammonium sulfide.[72]

Scheme 16. Amidrazone and Carboxylic Acid Precursors for the Synthesis of *N*-Acylamidrazones



Scheme 17. Synthesis of Triazole 70[a]



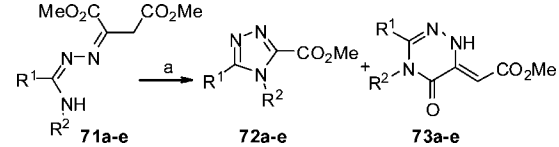
[a] Reagents and conditions: (a) *i*-BuOCOCl, NMM (*N*-methylmorpholine), THF; (b) (*E*)-*N*′-amino-*N*-phenylbenzamidine; (c) toluene, reflux, Dean−Stark trap.

Meanwell et al.[73] proposed to prepare triazole **70**, a potent inhibitor of ADP-induced aggregation of human platelets, from carboxylic acid **68** by coupling with the appropriate amidrazone followed by cyclization in refluxing toluene to give the target compound with a global yield of 56% (Scheme 17). Dehydration of the *N*-acylamidrazone **69** was performed under refluxing toluene using a Dean−Stark trap to facilitate the formation of the target triazole.

Modzelewska-Banachiewicz et al.[74] reported the cyclization of 2-[(1-arylamino-1-arylmethylidene)hydrazono]succinates **71a−e** to yield triazole compounds **72a−e** as potential antiviral agents (Table 11). Indeed, their virucidal action and effects on the replication of the selected strain RNA viruses [vesicular stomatitis virus (VSV), encephalomyocarditis virus (EMCV)] and DNA viruses [human adenovirus type 5 (AV5)] were investigated. This study revealed moderate activity of the triazole derivatives. Carrying out the cyclization reaction of **71a−e** in refluxing *n*-butanol yielded 1,2,4-triazole-5-carboxylic acid derivatives **72a−e** (with the liberation of a molecule of methyl acetate) and 5-oxo-1,2,4-triazine-6-carboxylic acid derivatives **73a−e** (with the liberation of methanol) in an approximately 1:1 ratio. Separation of both reaction products was possible based on their different solubilities in diethyl ether.

Modzelewska-Banachiewicz et al. worked on improving the triazole proportion. LeCount and co-workers had already described that reacting cyclic amidrazones with dimethyl acetylene dicarboxylate (DMAD) in methanol in the presence

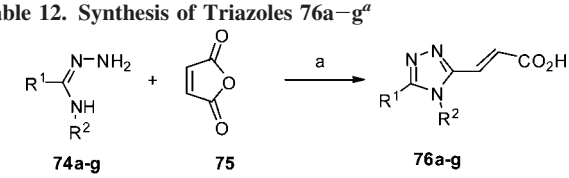
Table 11. Synthesis of Triazoles 72a−e[a]



72	R^1	R^2	yield (%) of 72
a	phenyl	phenyl	38
b	phenyl	4-methylphenyl	32
c	2-pyridyl	phenyl	35
d	2-pyridyl	4-methylphenyl	30
e	2-pyridyl	4-nitrophenyl	37

[a] Reaction conditions: (a) *n*-BuOH, reflux, 20 h.

Table 12. Synthesis of Triazoles 76a−g[a]



76	R^1	R^2	yield (%) of 76
a	phenyl	phenyl	72
b	2-pyridyl	phenyl	70
c	2-pyridyl	4-methylphenyl	70
d	2-pyridyl	4-nitrophenyl	50
e	2-pyridyl	2-pyridyl	50
f	4-pyridyl	phenyl	60
g	4-pyridyl	4-methylphenyl	70

[a] Reaction conditions: (a) Et_2O, room temperature, 48 h.

of triethylamine only led to derivatives of 5-hydroxy-1,2-pyrazole and 5-oxo-1,2,4-triazine.[75] Unfortunately, all additional trials failed to form 1,2,4-triazoles, and the triazinones were obtained in lower yields compared with methanol/triethylamine conditions.

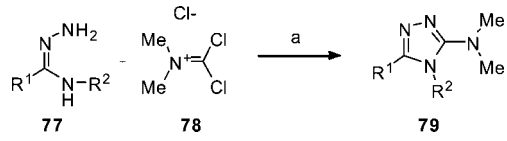
Regarding the mechanism, the key step consists of the nucleophilic attack of the amine. In methanol/triethylamine conditions, the addition−elimination on the methyl ester occurs, whereas in refluxing *n*-BuOH, a competition between the attack on the methyl ester and the imine occurs.

The same authors[76] described the synthesis and biological activity of 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid derivatives **76a−g** (Table 12). They were synthesized from N^3-substituted amidrazones **74a−g** by condensation with maleic anhydride **75** and isolated in 50−72% yields after precipitation and recrystallization. Here, the absence of competitive pathways can explain the better yields.

Zhang and co-workers developed a series of triazole-based opioid receptor antagonists.[77] The synthetic scheme was based on the formation of amidrazones prepared by reaction of thioamides with excess hydrazine at room temperature. Cyclization of amidrazones with different reagents led to the desired products through a *N*-acylamidrazone chemical equivalent. Some compounds, such as compounds **79**, were synthesized by cyclization of amidrazones **77** with phosgeninium salt **78** (Viehe's salt), which was obtained[78] from the corresponding amine (Scheme 18).

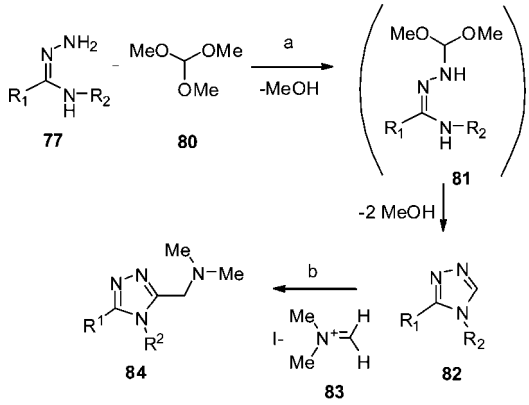
For SAR studies, Zhang et al.[77] wanted to optimize the distance between the triazole ring and the tertiary amine. They used a two-step reaction, first synthesizing 3,4-disubstituted triazoles **82** by reaction of amidrazones **77** with trimethyl orthoformate **80** and then performing an electro-

Scheme 18. Synthesis of Triazoles 79[a]



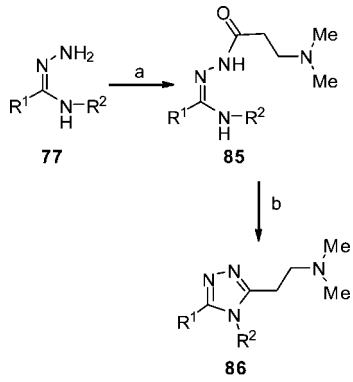
[a] Reaction conditions: (a) DCM, room temperature, 5 h.

Scheme 19. Synthesis of Triazoles 84[a]



[a] Reaction conditions: (a) Trimethylorthoformate, AcOH/DMF, room temperature; (b) DMF, 80 °C, 8 h.

Scheme 20. Synthesis of Triazoles 86[a]



[a] Reaction conditions: (a) 3-(*N*,*N*-dimethylamino)propionic acid hydrochloride, DCC, toluene, room temperature; (b) reflux, 8 h.

philic aromatic substitution with the Eschenmoser's salt[79] leading to **84** (Scheme 19).

Compounds **86** were directly prepared by condensation of amidrazones **77** with 3-(*N*,*N*-dimethylamino)propionic acid hydrochloride in the presence of dicyclohexylcarbodiimide in refluxing toluene (Scheme 20). No yields were reported for these syntheses.

2.1.3. *N*′-Acetyl-*N*,*N*-dimethylhydrazonamide Precursors

N′-Acetyl-*N*,*N*-dimethylhydrazonamides are also described as precursors of *N*-acylamidrazones (Scheme 21). As already shown for the synthesis of adamantyl-substituted triazoles **30**, oxadiazoles were reported as starting materials for triazole preparation.

Stocks et al.[80] proposed a one-pot synthetic method starting from dimethyl acetamide dimethyl acetal **87**, hydrazide **88**, and different aryl amines (Table 13). During this reaction, *N*′-acetyl-*N*,*N*-dimethylhydrazonamide intermediate **89** was formed and then condensed with the primary amine at high temperature in acidic media. Trisubstituted triazoles **90a**−**c** were obtained with good yields (55−69%), but in the study

Scheme 21. *N*′-Acetyl-*N*,*N*-dimethylhydrazonamide and Amine Precursors for the Synthesis of *N*-Acylamidrazones

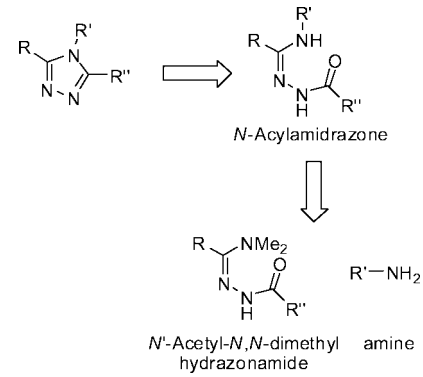
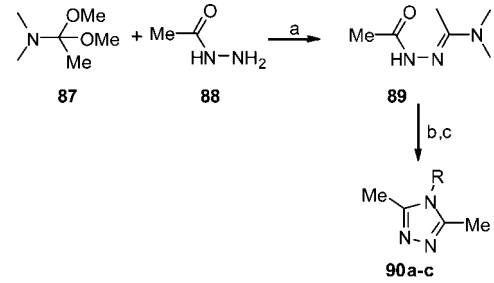


Table 13. Synthesis of Triazoles 90a−c[a]



90	R	yield (%) of 90
a	4-fluorobenzyl	69
b	phenyl	55
c	4-methoxyphenyl	60

[a] Reaction conditions: (a) CH_3CN, 50 °C, 30 min; (b) R-NH_2; (c) AcOH, 120 °C, 3 h.

examples were limited to triazoles bearing methyl substituents in positions 3 and 5.

Such a method was widely exemplified by Vanden Evnde and co-workers[81] for the synthesis of 3-(5-amino-1*H*-pyrazol-4-yl)-5-methyl-4*H*-1,2,4-triazoles.

Brown et al.[82] described the synthesis of an oxytocin receptor antagonist, based on the triazole moiety. This scaffold was synthesized by a two-step/one-pot reaction involving dimethyl acetamide dimethyl acetal **87** as reagent with an overall yield of 30%.

2.1.4. Oxadiazole Precursors

Oxadiazoles are well-known precursors of *N*-acylamidrazones. They are obtained via dehydration of *N*-acylhydrazides (Scheme 22).

Brown and Cheng[83] reported that 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles **91a**−**c** reacted with methylamine to produce 1,2-bis(*N*-alkylperfluoroalkylimidoyl)hydrazines **93a**−**c**. The authors suggested that this reaction occurs by attack of the nucleophilic amine on the electron-deficient oxadiazole ring carbon atom to afford the monoadducts **92a**−**c**. These intermediates underwent further reaction with the nucleophilic methylamine to provide only the bisadducts **93a**−**c**. Subsequently, compounds **93a**−**c** were thermally converted into the corresponding 4-substituted-3,5-bis(perfluoroalkyl)-4*H*-1,2,4-triazoles **94a**−**c** (Table 14).

Taking into account that the reaction of oxadiazoles with primary amines might be a general synthetic route to 4-substituted-3,4-bis(trifluoromethyl)-4*H*-1,2,4-triazoles, Re-

Scheme 22. Oxadiazole and Amine Precursors for the Synthesis of *N*-Acylamidrazones

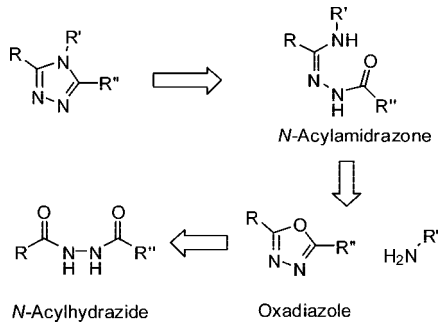
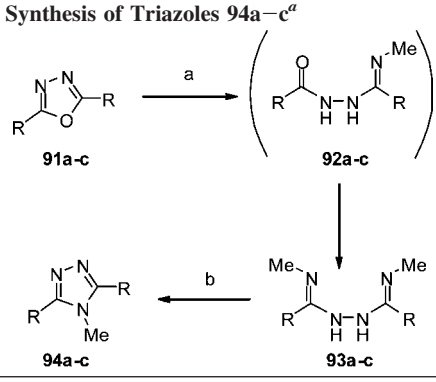


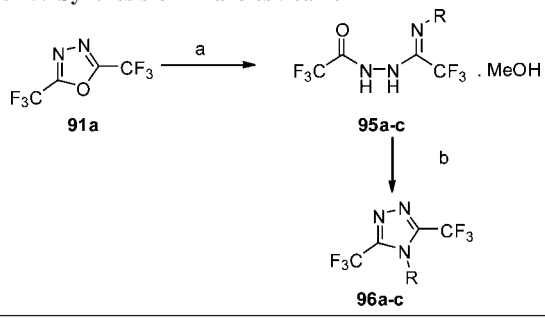
Table 14. Synthesis of Triazoles 94a−c[a]



94	R	yield (%) of 93	yield (%) of 94
a	trifluoromethyl	75	93
b	perfluoroethyl	quantitative	94
c	*n*-perfluoropropyl	95	88

[a] Reaction conditions: (a) $MeNH_2$, room temperature, 4 h in a sealed tube; (b) P_2O_5, 80 °C, 4 h.

Table 15. Synthesis of Triazoles 96a−c[a]

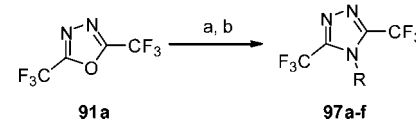


96	R	yield (%) of 95	yield (%) of 96
a (**94**a)	methyl	78	54
b	ethyl	90	56
c	2-butyl	95	39

[a] Reaction conditions: (a) R-NH_2, MeOH, −42 °C; (b) MeOH, reflux, 12−17 h.

itz et al.[30] investigated the scope and limitations of this reaction. In an attempt to moderate this reaction in order to isolate the monoadduct, the authors carried out the reaction in methanol at −42 °C in the presence of an excess of oxadiazole. The product isolated was a monoadduct with an incorporated molecule of methanol, i.e., hydrogen-bonded monoadduct−methanol complexes **95a−c**. Complexes **95a−c** were converted into the corresponding triazoles **96a−c** by stirring in methanol at reflux (Table 15).

Table 16. Synthesis of Triazoles 97a−f[a]



.

97	R	yield (%) of 97
a	*n*-propyl	83
b	*i*-butyl	70
c	3-prop-1-enyl	26
d	*n*-butyl	40
e	cyclohexyl	52
f	4-chlorophenylmethyl	72

[a] Reaction conditions: (a) R-NH_2, −78 to −30 °C then room temperature or reflux; (b) MeOH, reflux.

However, isolation of complexes **95a−c** prior to cyclization proved to be unnecessary for the preparation of 4-alkyltriazoles **96a−c**. Acceptable yields of 4-alkyltriazoles were isolated without the use of an excess of oxadiazole or the use of methanol as solvent to moderate the reaction. Examples of other synthesized 4-alkyl-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles **97a−f** are listed below (Table 16).

The reaction of oxadiazole **91a** with substituted anilines in refluxing methanol proceeded smoothly and generally provided 4-aryl-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles **98a−s** in moderate to good yields. However, when the aromatic amine had a strong electron-withdrawing substituent (i.e., CF_3) in either the 2 or 4 position or when it had several moderate electron-withdrawing substituents (i.e., Cl), 4-aryltriazoles were not produced in refluxing methanol. The reaction also proved to be sensitive to steric hindrance. Examination of models revealed that to yield triazoles **98a−s**, the aromatic ring must rotate out of the plane of the triazole ring so that the two trifluoromethyl groups at the 3,5 positions do not sterically interfere with the two substituents in the 2,6 positions of the aromatic ring. Assuming that these difficulties could be surmounted by higher reaction temperatures, oxadiazole **91a** and 2-trifluoromethylaniline were heated 24 h at 115 °C in a sealed glass tube to give the expected triazole **98j** in 34% yield after recrystallization (Table 17).

Kakefuda et al.[60] also described the synthesis of 1,2,4-triazoles **102a−c** as selective V_{1A} receptor antagonists via reaction of oxadiazoles **101a−c** with amines (Table 18). In this case, the obtained yields were modest (12−31%).

Carlsen et al.[84] proposed the reaction of 2,5-disubstituted 1,3,4-oxadiazole **105** with amines to give the desired unsymmetrical compounds **106a**,**b**. Indeed, the appropriate acylhydrazide **104** was prepared by acylation of benzoylhydrazide **103** with acetyl chloride. This unsymmetrical acylhydrazide **104** was then heated with an excess of neat phosphorus pentoxide at 100 °C for 24 h without solvent to give the desired oxadiazole **105** in 55−83% yields. Heating the 1,3,4-oxadiazole with allyl- or benzylamine in sealed tubes at 150 °C for 2−12 days resulted in formation of the desired triazoles **106a**,**b** in acceptable yields after flash column chromatography or recrystallization (Table 19). The reactions may be carried out in inert solvents such as benzene or toluene or without any solvent.

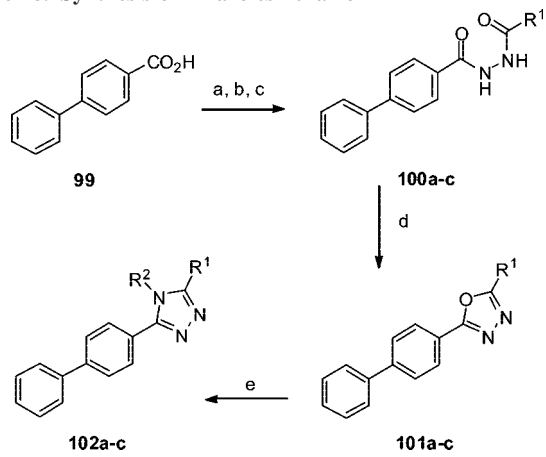
Garcia and co-workers synthesized a series of bistriazoles **110a−e** as positive modulators of adrenomedullin.[85] Phenoxyacetic acid was treated with the corresponding commercially available dihydrazides **107a−e** in the presence of

Table 17. Synthesis of triazoles 98a−s

91a 98a-s

98	R	reaction conditions	yield (%) of **98**
a	4-methoxyphenyl	RNH_2, MeOH, 0 °C then 17 h room temperature	76
b	3-methoxyphenyl	RNH_2, MeOH, 0 °C then 18 h room temperature	52
c	2-methoxyphenyl	RNH_2, MeOH, 0 °C then 65 h room temperature	65
d	4-methylphenyl	RNH_2, MeOH, 0 °C then 19 h room temperature	40
e	3-methylphenyl	RNH_2, MeOH, 0 °C then 120 h room temperature	74
f	2-methylphenyl	RNH_2, MeOH, 0 °C then 45 h room temperature	61
g	phenyl	RNH_2, reflux, 24 h	66
h	4-trifluoromethylphenyl	RNH_2, sealed tube, 120 °C, 14 h	29
i	3-trifluoromethylphenyl	RNH_2, reflux, 110 h	73
j	2-trifluoromethylphenyl	RNH_2, sealed tube, 125 °C, 72 h	34
k	4-fluorophenyl	RNH_2, MeOH, 0 °C then 24 h room temperature	67
l	3-fluorophenyl	RNH_2, reflux, 29 h	37
m	4-chlorophenyl	RNH_2, reflux, 22 h	32
n	2,4-dichlorophenyl	RNH_2, sealed tube, 140 °C, 24 h	54
o	3,4-dichlorophenyl	RNH_2, reflux, 69 h	50
p	2,4,5-trichlorophenyl	RNH_2, sealed tube, 140 °C, 48 h	46
q	2,6-dimethylphenyl	RNH_2, sealed tube, 150 °C, 72 h	75
r	2,6-diethylphenyl	RNH_2, sealed tube, 150 °C, 72 h	37
s	3,5-di(trifluoro)phenyl	RNH_2, reflux, 137 h	39

Table 18. Synthesis of Triazoles 102a−c[a]

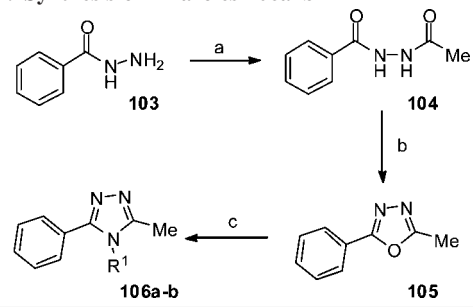


99 100a-c 101a-c 102a-c

102	R^1	R^2	yield (%) of **102**
a	Me	2-methoxyphenyl	31
b	H	2-methoxyphenyl	12
c	Me	2-methoxybenzyl	28

[a] Reaction conditions: (a) $SOCl_2$, DMF cat., THF; (b) $NH_2NH_2.H_2O$, THF; (c) R^1CO_2COMe, pyridine; (d) P_2O_5, toluene, reflux; (e) R^2NH_2, 150 °C.

Table 19. Synthesis of Triazoles 106a–b[a]



103 104 105 106a-b

106	R^1	yield (%) of **106**
a	allyl	58[b]
b	benzyl	99[c]

[a] Reaction conditions: (a) MeCOCl, Et_3N, THF, reflux, 3 h; (b) P_2O_5, 110 °C, 22 h; (c) R^2NH_2, 150 °C. [b] Yield after recrystallization. [c] Yield of the crude product.

$POCl_3$ to yield compounds **108a−e**. Further refluxing of these intermediates with $POCl_3$ in acetonitrile for 7 h gave bisoxadiazoles **109a−e**. Finally, reaction with benzylamine yielded the desired bistriazoles **110a−e** (Table 20).

Li et al.[86] used a similar methodology for the synthesis of bipolar oligofluorenes with light-emitting properties by directly converting hydrazides into the corresponding triazoles in a one-pot reaction. Brown et al. also used this method for the synthesis of oxytocin receptor antagonists.[87]

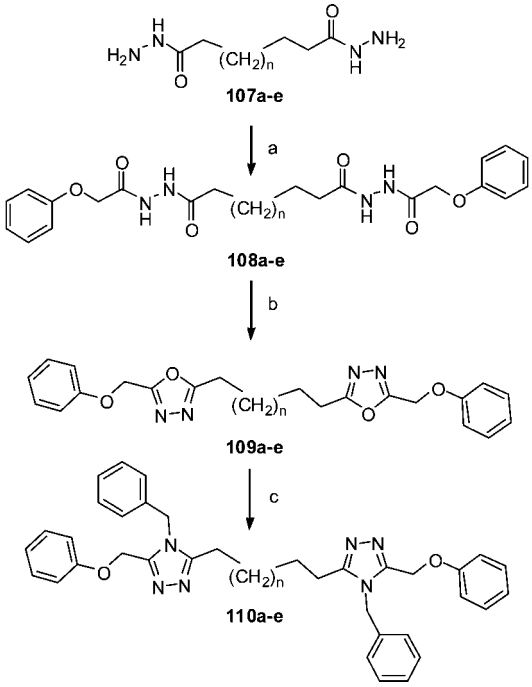
The numerous previously described examples lead to a comparison of the influence of the substituents carried by the oxadiazole ring during amine nucleophilic attack. Indeed, we notice that reaction with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazoles proceeded in milder conditions and better yields. Other bis(perfluoroalkyl)-substituted oxadiazoles reacted in the same way. To our knowledge, all other tested substituents led to a decrease in the obtained yields. It appears that strong electron-withdrawing substituents thus facilitate nucleophilic attack on the electron-deficient oxadiazole carbon atom.

2.1.5. N-Methyl-N-nitrosoamidine Precursors

N-Methyl-*N*-nitrosoamidines are also described to be activated precursors of *N*-acylamidrazones (Scheme 23).

Fustero et al.[88] described *N*-methyl-*N*-nitrosoamidines **111a−c** as synthetic equivalents of imidoylchlorides, the N(NO)Me group being the leaving group. Nucleophilic substitution by acetic acid hydrazide afforded the corresponding *N*-acylamidrazones, which were then cyclized upon heating in DMF in the presence of *p*-TsOH to afford triazole-fused 1,4-benzodiazepines **112a−c** in good yields (Table 21). Although this reaction has previously been reported in the literature for the formation of the *N*-oxide derivative of **112b**,[89] the final tricyclic system could not be isolated but rather appeared along with another uncyclized product. The use of *p*-TsOH in the cyclization step greatly increases the

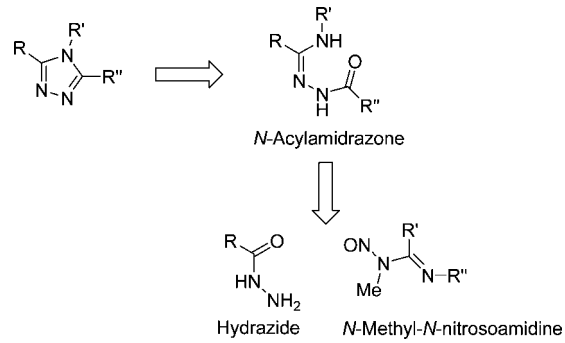
Table 20. Synthesis of Compounds 110a−e[a]



110	*n*	yield (%) of **108**	yield (%) of **109**	yield (%) of **110**
a	1	16	76	30
b	2	23	59	22
c	3	36	28	27
d	4	23	63	51
e	5	25	70	42

[a] Reaction conditions: (a) Phenoxyacetic acid, $POCl_3$, CH_3CN, heating; (b) $POCl_3$, CH_3CN, reflux; (c) benzylamine, heating.

Scheme 23. Hydrazide and *N*-Methyl-*N*-nitrosoamidine Precursors for the Synthesis of *N*-Acylamidrazones



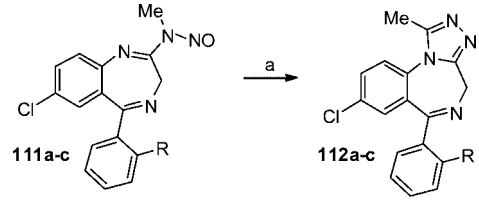
efficiency of this process as it enables the complete conversion of the starting material, thereby improving the final yield.

2.1.6. Arylphosphazoanilide Precursors

Formation of 3,4,5-triaryltriazoles from acylhydrazides is a well-known reaction. Busch,[90] for example, recommended phosphorus pentoxide as a catalyst, but it gave modest yields. Bhagat and Rây[91] prepared several triaryltriazoles by fusing dibenzoylhydrazine with an amine in the presence of zinc chloride, but no yields were reported. Klingsberg[92] used arylphosphazoanilides (Scheme 24).

Arylphosphazoanilides **114a−g** were prepared from phosphorus trichloride and aromatic amines **113a−g**. Then, heating **114a−g** in situ at reflux with acylhydrazides yielded

Table 21. Synthesis of Compounds 112a−c[a]



112	R	yield (%) of **112**
a	F	84
b	H	87
c	Cl	81

[a] Reaction conditions: (a) $MeCONHNH_2$, TsOH, DMF, 120 °C, 1 h.

Scheme 24. *N*-Acylhydrazide and Arylphosphazoanilide Precursors for the Synthesis of *N*-Acylamidrazones

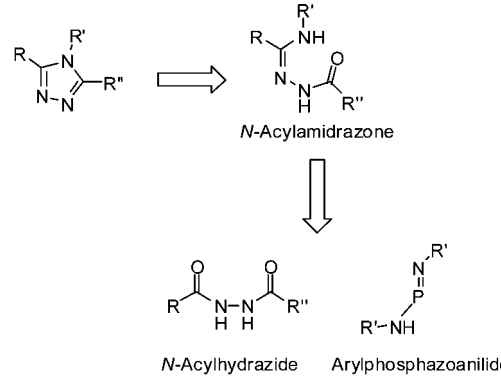
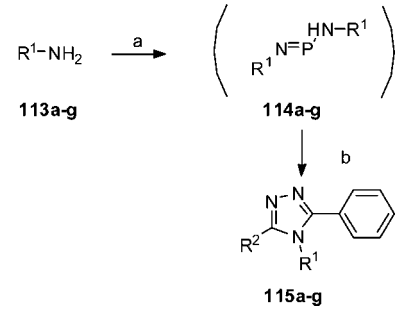


Table 22. Synthesis of Triazoles 115a−g[a]



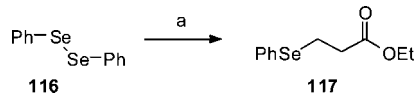
115	R^1	R^2	crude yield (%) of **115**
a	phenyl	phenyl	95
b	4-methylphenyl	phenyl	88
c	2-methylphenyl	phenyl	72
d	3-methylphenyl	phenyl	83
e	4-chlorophenyl	phenyl	88
f	phenyl	4-pyridyl	95
g	2-naphtyl	phenyl	52

[a] Reaction conditions: (a) PCl_3, *o*-dichlorobenzene, room temperature; (b) $R_2CONHNHCOPh$, reflux, 3 h.

the desired triazole compounds **115a−g** with good yields (Table 22). Klingsberg failed to transfer this methodology to the synthesis of alkyl-substituted triazoles.

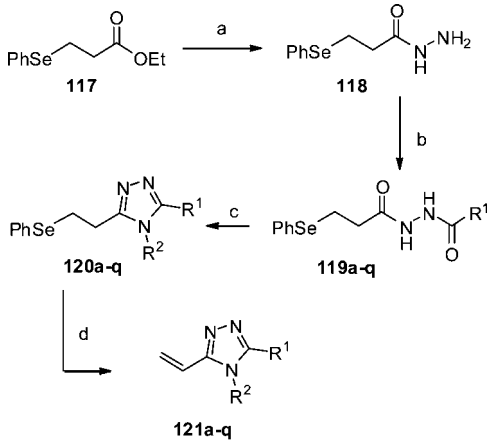
Wang and co-workers described a similar method involving arylphosphazoanilide precursors and key organoselenium reagents.[93] The introduction of these organoselenium reagents was greatly attractive since it allowed easy access to vinyl-substituted 1,2,4-triazoles which are otherwise difficult to synthesize due to the tedious preparation of α,β-unsaturated hydrazides. Diphenyl diselenide **116** was treated with $NaBH_4$

Scheme 25. Synthesis of Ethyl 3-Phenylselanyl Propionate 117[a]



[a] Reaction conditions: (a) $NaBH_4$, THF/DMF, room temperature, 8 h; $ClCH_2CH_2COOEt$, room temperature, 4 h.

Table 23. Synthesis of Triazoles 121a−q[a]



121	R^1	R^2	yield (%) of **120** based on **117**	yield (%) of **121**
a	Phenyl	2-Methylphenyl	71	96
b	Phenyl	3-Methoxyphenyl	62	95
c	phenyl	2,4-dimethylphenyl	68	97
d	phenyl	4-chlorophenyl	73	98
e	benzyl	4-methylphenyl	80	97
f	benzyl	phenyl	79	98
g	4-methoxyphenyl	4-methylphenyl	71	96
h	4-methoxyphenyl	2-methylphenyl	67	97
i	4-methoxyphenyl	4-chlorophenyl	72	97
j	methyl	4-methylphenyl	82	98
k	methyl	1-naphthalenyl	70	97
l	methyl	3-methoxyphenyl	59	97
m	*i*-propyl	phenyl	70	96
n	*i*-propyl	4-methylphenyl	69	97
o	*i*-propyl	2-methylphenyl	65	98
p	*n*-hexyl	3-methylphenyl	71	97
q	*n*-hexyl	2-methylphenyl	63	97

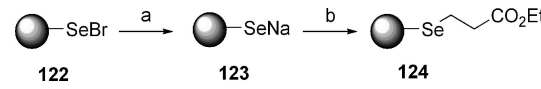
[a] Reaction conditions: (a) $NH_2NH_2 \cdot H_2O$, MeOH, reflux; (b) R^1COCl, pyridine, DCM, 0 °C then room temperature; (c) $R^2-N=P-NH-R^2$, *o*-dichlorobenzene, reflux, 3 h; (d) H_2O_2, THF, 10 min at 0 °C then 1.5 h at room temperature.

and ethyl 3-chloropropionate to yield ethyl 3-phenylselanyl propionate **117** almost quantitatively (Scheme 25).

Since the direct reaction of phenylselanyl propionate and hydrazide did not occur, a two-step reaction was adopted to synthesize acylhydrazides **119**: hydrazinolysis of the ethyl propionate **117** followed by acylation of the obtained hydrazide **118** by an acyl chloride. Acylhydrazides **119** can undergo a cyclocondensation reaction with arylphosphazoanilides to yield to phenylselanylethyl-substituted 1,2,4-triazoles **120a−q**. After selenoxide *syn*-elimination, vinyl-substituted 1,2,4-triazoles **121a−q** could be obtained in good yields regardless of whether R^1 is alkyl or aryl and R^2 is aryl carrying an electron-donating group or an electron-withdrawing group (Table 23).

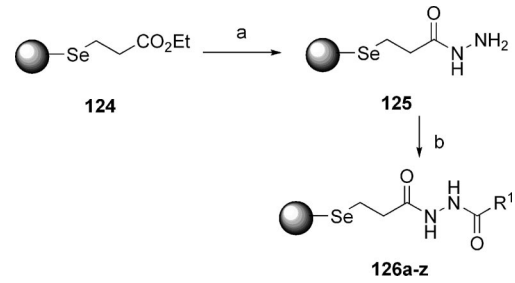
This method was also performed on solid support: the same research group described the preparation of a library of vinyl-substituted 1,2,4-triazoles using an organoselenium resin.[94]

Scheme 26. Synthesis of Resin-Bound Ethyl Propionate[a]



[a] Reaction conditions: (a) $NaBH_4$, THF/DMF, room temperature, 10 h; (b) $ClCH_2CH_2CO_2Et$, room temperature, 5 h.

Scheme 27. Acylhydrazination of the Supported Ester[a]



[a] Reaction conditions: (a) $NH_2NH_2.H_2O$, MeOH, 24 h; (b) R^1COCl, pyridine, DCM, 0 °C then room temperature, 12 h.

The first organoselenium resin was reported in 1976.[95] Nicolaou[96] and Ruhland[97] reported independently a variety of organoselenium resins carrying convenient easily cleavable linkers and with versatile reactivity that were efficiently used for the synthesis of natural products. More recently, some groups have been interested in the preparation of heterocyclic libraries from organoselenium resins.[98−106] Resin-bound ethyl propionate **124** was prepared by treatment of a THF/DMF-swollen suspension of resin **122** with $NaBH_4$ for 10 h followed by treatment with ethyl 3-chloropropionate for an additional 5 h (Scheme 26). FT-IR showed a strong carbonyl absorption at 1734 cm^{-1}.

With this resin in hand, the authors investigated the acylhydrazination reaction. A two-step reaction was adopted because no direct reaction could occur between resin and hydrazides (Scheme 27). First, resin-based reagent **124** was reacted with hydrazine hydrate in MeOH for 24 h to obtain resin **125** (FT-IR showed a band at 1640 cm^{-1} with disappearance of the band at 1734 cm^{-1}). Second, resin **125** was smoothly reacted with an acyl chloride, and the FT-IR spectra of resins **126a−z** showed that the band of the strong carbonyl absorption moved to about 1590 cm^{-1} because of the conjugative effect.

The cyclocondensation reaction leading to 1,2,4-triazoles **127a−z** proceeded smoothly with arylphosphazoanilides. After the selenoxide *syn*-elimination of resin, the 3-vinyl-1,2,4-triazoles **128a−z** can be obtained in moderate yields with good purities regardless of whether R^1 is alkyl or aryl and R^2 is aryl carrying an electron-donating group or an electron-withdrawing group (Table 24).

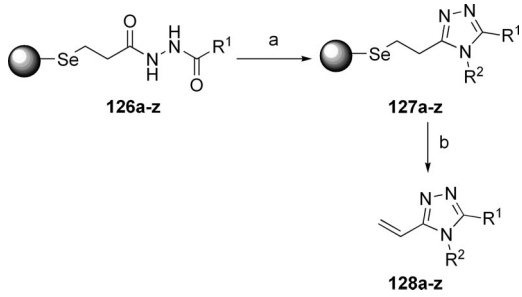
2.2. Specific Methods

Some studies reported on the synthesis of 1,2,4-triazoles bearing specific functionalities or substituents using *N*-acylamidrazone as an intermediate.

2.2.1. Synthesis of 1,2,4-Triazole-3-carboxylates via Methyleneiminium Salts

Bartholomew et al.[107] used methyleneiminium salts as intermediates for the synthesis of 1,2,4-triazoles via a 1-acyl-3-carboxy-4-alkylamidrazone intermediate. This acyclic intermediate **130** was isolated in 56% yield, and its cyclization yielded the desired product **131** in 53% yield (Scheme 28).

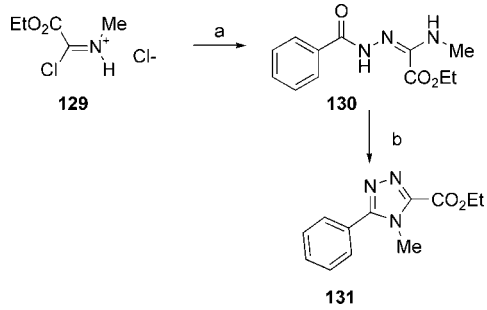
Table 24. Synthesis of Triazoles 128a−z[a]



128	R^1	R^2	yield[b] (%) of **128**	purity[c] (%)
a	methyl	phenyl	65	90
b	methyl	3-methylphenyl	61	92
c	methyl	2,4-dimethylphenyl	51	89
d	methyl	4-chlorophenyl	60	89
e	methyl	3-methoxyphenyl	61	90
f	methyl	α-naphthalenyl	53	85
g	phenyl	phenyl	63	87
h	phenyl	4-methylphenyl	61	91
i	phenyl	3-methylphenyl	61	90
j	phenyl	4-chlorophenyl	59	94
k	phenyl	3-methoxyphenyl	57	89
l	benzyl	2-methylphenyl	54	89
m	benzyl	2,4-dimethylphenyl	55	93
n	benzyl	4-chlorophenyl	59	91
o	benzyl	3-methoxyphenyl	61	89
p	4-methoxyphenyl	phenyl	64	92
q	4-methoxyphenyl	3-methylphenyl	60	89
r	4-methoxyphenyl	2,4-dimethylphenyl	56	85
s	4-methoxyphenyl	4-chlorophenyl	61	90
t	*n*-hexyl	phenyl	69	93
u	*n*-hexyl	4-methylphenyl	67	91
v	*n*-hexyl	2,4-dimethylphenyl	60	88
w	*n*-hexyl	4-chlorophenyl	62	90
x	*i*-propyl	3-methylphenyl	59	86
y	*i*-propyl	2,4-dimethylphenyl	49	92
z	*i*-propyl	4-chlorophenyl	58	89

[a] Reaction conditions: (a) $R^2-N=P-NH-R^2$, *o*-dichlorobenzene, 4 h; (b) H_2O_2, THF, 0 °C, 10 min then room temperature, 1.5 h. [b] Yield of the crude products is based on the loading of the resin. [c] Purity of the crude products was determined by HPLC at 254 nm.

Scheme 28. Synthesis of Triazole 131[a]



[a] Reaction conditions: (a) $PhCONHNH_2$; (b) toluene, reflux.

2.2.2. Synthesis of 2-(1,2,4-Triazol-4-yl)benzoic Acids from 1,3-Benzoxazines

Deshmukh et al.[108] proposed using 1,3-benzoxazines as intermediates for the synthesis of 1,2,4-triazoles (Scheme 29).

A first step involves condensation of anthranilic acid **132** with benzoyl chloride **133**. After isolation of the 1,3-benzoxazine **134** by precipitation, it was reacted with hydrazides to give the target compounds **135a**,**b** in about 60% yields (Table 25). These compounds were tested to determine their antimicrobial activity against some Gram-positive and Gram-negative pathogenic bacterial and fungal species like *E. coli*, *P. valgarism*, *B. subtilis*, *S. aurius*, *A. niiger*, and phytophota species. This study revealed moderate to good antimicrobial activity of the triazole derivatives against the above-mentioned species.

Scheme 29. 1,3-Benzoxazine Precursors for the Synthesis of *N*-Acylamidrazones

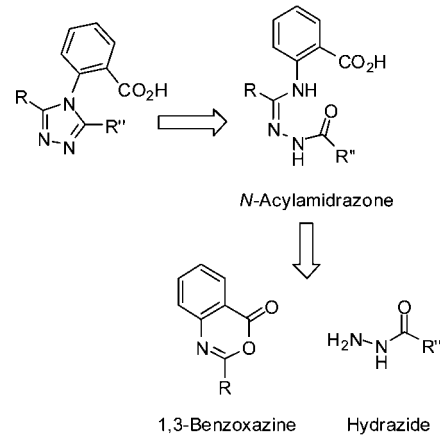
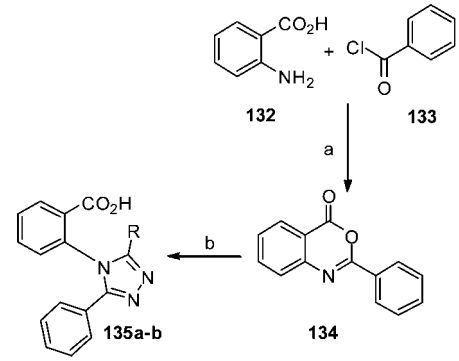


Table 25. Synthesis of Triazoles 135a–b[a]



135	R	yield (%) of **135**
a	2-chlorophenyl	60
b	2-tolyloxymethyl	64

[a] Reaction conditions: (a) Pyridine, room temperature, 30 min; (b) $RCONHNH_2$, MeOH, reflux, 1 h.

2.2.3. Synthesis of 2-(1,2,4-Triazol-4-yl)but-2-enoic Acids from Oxazolones

Maekawa et al.[109] proposed a new method for the synthesis of 1,2,4-triazoles, starting from (*Z*)-2-methyl-4-arylmethylene-5(4*H*)-oxazolones and hydrazides (Scheme 30).

The ring-opening mode of these oxazolones with hydrazides was investigated from both synthetic and mechanistic points of view. It was found that the novel ring-opening reaction produced 1,2,4-triazole-substituted (*Z*)-α-dehydroamino acids **138a−c** in high yields, irrespective of the substituents and solvents examined. It was also suggested that the triazole ring is constructed via the preferential nucleophilic addition of the hydrazino nitrogen to the C−N double bond in the oxazolone rings **136a−c** to give the *N*-acylamidrazone intermediates (Table 26).

2.2.4. Synthesis of 1-(5-Chloro-2-(1,2,4-triazol-4-yl)phenyl)ketones from Quinazolines

Hirai et al.[110] used quinazoline precursors for the synthesis of 1,2,4-triazoles (Scheme 31).

Scheme 30. Oxazolone Precursors for the Synthesis of *N*-Acylamidrazones

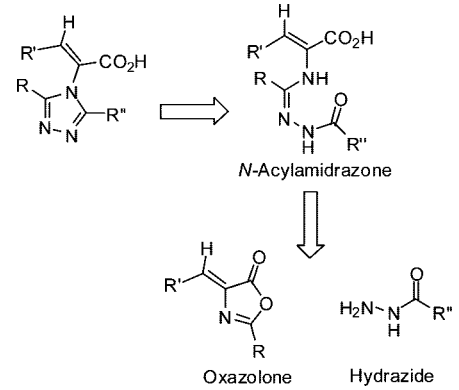
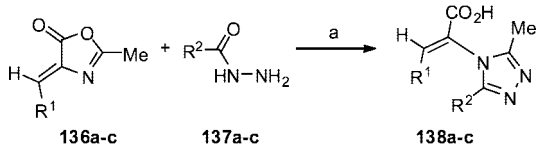


Table 26. Synthesis of Triazoles 138a−c[a]



138	R^1	R^2	yield (%) of **138**
a	phenyl	benzyl	75
b	phenyl	4-nitrophenyl	92
c	1-naphthyl	methyl	90

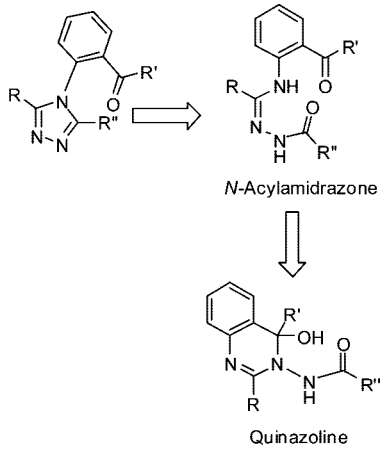
[a] Reaction conditions: (a) MeCN, reflux, 1 h.

The fusion of a triazole ring to the amide moiety of a 1,4-benzodiazepine is known to be useful for imparting enhanced potency and novel activity to the parent benzodiazepine.[111] The authors were interested here in the synthesis and pharmacological activities of ring-opened derivatives of triazolobenzodiazepines **140**. These compounds were in fact considered as water-soluble prodrugs which could undergo an enzymatic hydrolysis of the peptide bond followed by a chemical cyclization in physiological conditions to give the triazolobenzodiazepine scaffold **139** (Scheme 32). As an example, Cho et al.[112] reported the use of a reversible 1,4-benzodiazepine ring-opening reaction of Alprazolam.

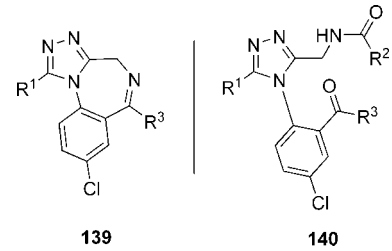
The key step of the synthesis was the treatment of quinazolines **141** with AcOH to obtain the target triazoles **140** (Scheme 33).

The yields for this cyclization step are not mentioned in the experimental part (only the global yields for the whole synthetic scheme are indicated: from 13% to 91%). These compounds were tested to determine their antianxiety, anticonvulsant, and sedative activities as 1,4-benzodiazepine analogues.

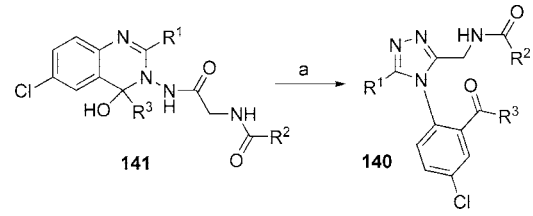
Scheme 31. Quinazoline Precursors for the Synthesis of *N*-Acylamidrazones



Scheme 32. Triazolobenzodiazepine Scaffold 139 versus Its Prodrug 140

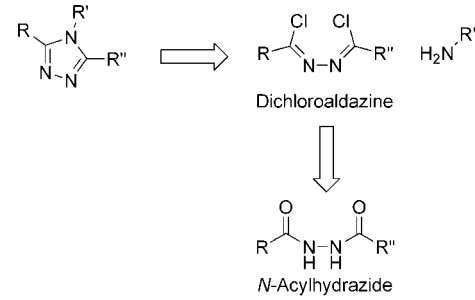


Scheme 33. Synthesis of Triazoles 140[a]



[a] Reaction conditions: (a) AcOH, reflux.

Scheme 34. Triazole Synthesis via Dichloroaldazine intermediates



3. Synthesis via Other Intermediates

Apart from *N*-acylamidrazones, other intermediates can be used, such as dichloroaldazines and triazolopyrazines.

3.1. General Method

Dichloroaldazines are versatile and well-known intermediates for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles.

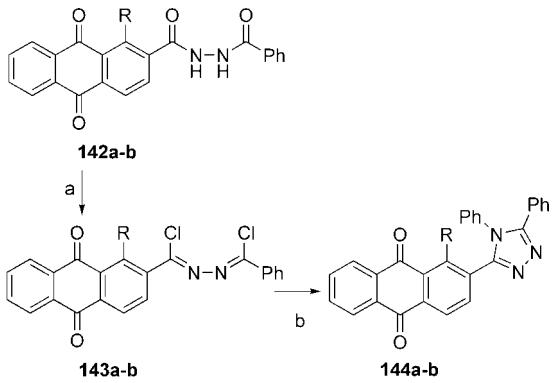
3.1.1. Dichloroaldazine Intermediates

The use of dichloroaldazines, derived from *N*-acylhydrazides, is a viable route leading to trisubstituted 1,2,4-triazoles (Scheme 34).

Klingsberg et al.[113] described the conversion of *N*-acylhydrazides **142a**,**b** into the corresponding dichloroaldazines **143a**,**b** followed by the reaction with aniline to form trisubstituted triazoles **144a**,**b** bearing an anthraquinone moiety (Scheme 35). However, no yields were reported by the authors.

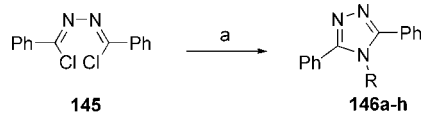
Gautun et al.[114] further examined this method (Table 27) and demonstrated that it is a viable route to synthesize hindered 4-alkyltriazoles **146a**−**h** that are otherwise difficult to obtain.

Scheme 35. Synthesis of Triazoles 144a–b[a]



[a] Reaction conditions: (a) PCl_5, 145 °C; (b) $PhNH_2$, 170 °C.

Table 27. Synthesis of Triazoles 146a−h[a]



146	R	solvent	yield (%) of 146
a	methyl	methylamine	60
b	ethyl	ethylamine	84
c	1-propyl	propylamine	69
d	2-propyl	2-propylamine	30
e	2-butyl	*N*,*N*-dimethylaniline	87
f	cyclohexyl	benzene	48
g	1-octyl	benzene	79
h	2-octyl	2-octylamine	95

[a] Reaction conditions: (a) RNH_2, solvent, heating.

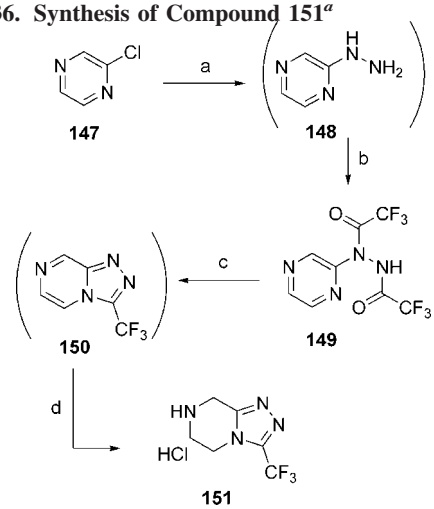
3.2. Specific Method

A specific triazolopiperazine scaffold can be obtained from triazolopyrazines.

3.2.1. Synthesis of Triazolopiperazines from Triazolopyrazines

Hansen et al.[115] described the synthesis of Sitagliptin (MK-0431 or JANUVIA), a dipeptidyl peptidase IV enzyme inhibitor, for the potential treatment of type II diabetes, suitable for the preparation of multikilogram quantities. The triazolopiperazine fragment **151** of Sitagliptin was prepared in 26% yield over four reaction steps (Scheme 36).[116,117] Key process developments were made in the first step of this sequence, the addition of hydrazine to chloropyrazine, to ensure its safe operation on a large scale.

Scheme 36. Synthesis of Compound 151[a]



[a] Reaction conditions: (a) 35% $NH_2NH_2 \cdot H_2O$; (b) trifluoroacetic anhydride, 49% yield for the two first steps; (c) superphosphoric acid, 75 °C; (d) H_2, Pd/C then HCl, *i*-PrOH, 51% yield for the two last steps.

4. Conclusion

In this paper, we described the state of the art in the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles. As disubstituted triazoles have been widely used as pesticides and antifungic agents, trisubstituted triazoles are now extensively studied in medicinal chemistry and biochemistry. A lot of work has already been done concerning the synthesis of this scaffold. For chemists working with amino-acid precursors, the synthesis developed by Boeglin et al. would be very useful as it leads to an optically pure trisubstituted triazole and allows a wide variety of substituents. For chemists who need specific substitutions, for example, dimethylalkylamines and vinyl derivatives, more dedicated methods allowing one to quickly obtain libraries of compounds will be of great interest. The large number of examples we found both in academic and patent literature convinced us that 1,2,4-triazoles can be a scaffold of choice for the design of new potentially bioactive compounds. First, the use of general synthetic methods can enable the introduction of various substituents during the first step, resulting in the discovery of a lead molecule. Second, more specific methods can be optimized for rapid generation of focused libraries, especially with the help of parallel and solid-supported synthesis. Owing to the importance of the potential applications of these compounds, we believe that chemists will continue their research in this field.

5. References

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