Advances in the synthesis and reactivity of acyl azides (2005-2015)

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Avances en la síntesis y reactividad de las azidas de acilo (2005-2015)

Avanços en la síntesi i reactivitat de les azides d'acil (2005-2015)

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SUMMARY

This review article presents an overview of major synthetic approaches and applications of acyl azides chemistry. We, herein, report various methodologies for the synthesis of acyl azides and their synthetic applications/consecutive reactions attempted since 2005.

Keywords: Acyl azides; azides; carbamates; urea derivatives; urethanes

RESUMEN

Este artículo a modo de reseña presenta una visión global de los principales métodos sintéticos y aplicaciones de la química de los azidas de acilo. Informamos aquí sobre las diversas metodologías para la síntesis de los azidas de acilo y sus aplicaciones sintéticas/reacciones consecutivas conseguidas desde el año 2005.

Palabras clave: Azidas de acilo; azidas; carbamatos; derivados de urea; uretanos.

RESUM

Aquest article resum presenta una visió global dels principals mètodes sintètics i aplicacions de la química dels azides d'acil. Els informem aquí de les diverses metodologies per la síntesi d'azides d'acil i les seves aplicacions sintètiques/reaccions consecutives des de l'any 2005.

Paraules clau: Azides d'acil; azides; carbamats; derivats d'urea; uretans

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INTRODUCTION

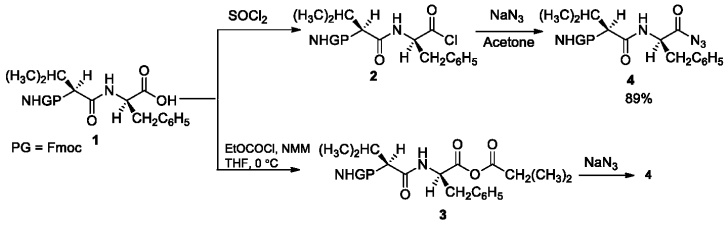
Acyl azides (R-CO-N_3) belong to energy rich and synthetically important class of organic azides which have gained considerable interest due to their versatility as well as high reactivity[1]. A variety of methods are used to introduce azido group into organic compounds[2]. In general, acyl azides are achieved via the treatment of acid hydrazides, acid chlorides or acyl benzotriazoles with azide ion or by in situ activation of carboxylic acids using azide ion[3]. Moreover, literature reveals different methods to access acyl azides from aldehydes by using suitable reagents[4]. Acyl azides undergo Curtius rearrangement which is of paramount value in the synthesis of many biologically active molecules as well as natural products[5,6].

Owing to the great reactivity and applications of azides, Brase *et al* [3] in 2005, Yubo *et al*[7] in 2012, Tanimoto and Kakiuchi[8] in 2013 and Intrieri[19] in 2014 have published review articles on accounts of organic azides. However, to the best of our knowledge, an independent review on the developments of synthetic approaches as well as important consecutive applications of acyl azides is not yet reported. This review article will depict some of the recent synthetic methodologies and applications of acyl azides reported during the last ten years.

REVIEW OF LITERATURE

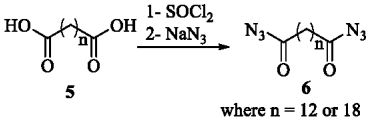
Synthesis of Acyl Azides

Various scientists have prepared acyl azides and transformed them into biologically important compounds. In 2005, Babu et al synthesized N^{α}-Fmoc-peptide acid azides **4** by the treatment of N^{α}-Fmoc-peptide acid chloride **2** with sodium azide without Curtius rearrangement[10]. Same reaction was performed using mixed anhydride **3** method which appeared to be a good alternative for peptides having acid labile protecting groups such as t-butyl and trityl groups (Scheme 1). Various N^{α}-Fmoc-peptide acid azides were prepared containing different functional groups with 75-92% yield. Further, N^{α}-Fmoc-peptide acid azides were utilized as coupling agents in the extension of the peptide chain in good yields.



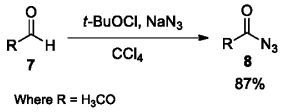
Scheme 1. *Synthesis of N^{α}-Fmoc-peptide acid azide 4.*

During their study on triazole-oligomers, Katritzky and coworkers, in 2006, prepared dicarboxyl azide **6** by the treatment of dicarboxylic acid **5** with thionyl chloride followed by the reaction of intermediate acid chloride with sodium azide (Scheme 2) [11].



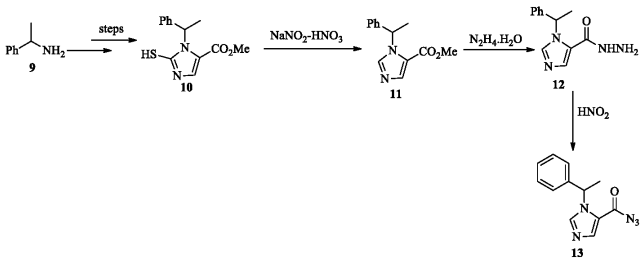
Scheme 2. *Synthesis of dicarboxyl azide 6.*

Aldehydes act as good precursors for acyl azides. In 2007, Arote and Akamanchi reported the direct conversion of aliphatic, aromatic and heteroaromatic aldehydes 7 into corresponding acyl azides **8** using *t*-BuOCl and NaN_3 under mild reaction conditions in 72-87% yields (Scheme 3) [12].



Scheme 3. *Synthesis of acyl azides **8** using tert-butyl hypochlorite.*

Bright and co-workers, in 2007, prepared acyl azide **13** from etomidate[13]. The acyl azide **13** was analogue of etomidate and could be used as photolabel to check the binding sites of etimodate. In their methodology, methyl benzylamine **9** was converted to thiol **10** over a series of steps. The compound **10** upon oxidative desulfurization with nitric acid-sodium nitrite yielded methyl ester **11** which upon treatment with hydrazine hydrate formed hydrazide **12**. Treatment of hydrazide **12** with nitrous acid afforded acyl azide **13** in reasonable yield (Scheme 4).

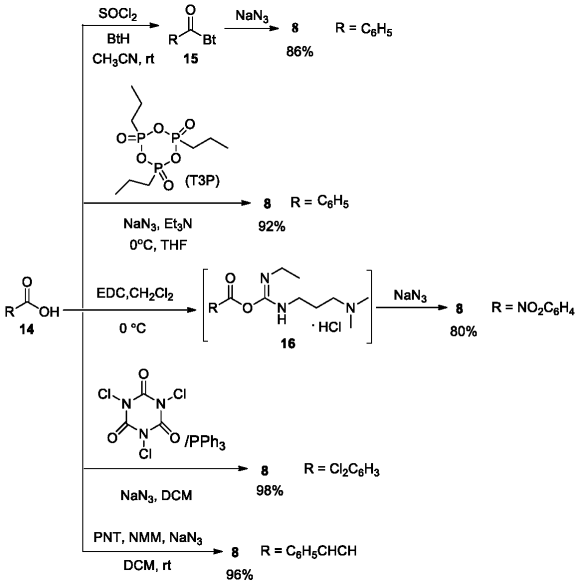


Scheme 4. *Preparation of acyl azide 13 from etomidate.*

Katritzky et al in 2007, employed the use of N-acylbenzotriazoles **15** towards the synthesis of different acyl azides **8** in good yields avoiding Curtius rearrangement and racemization[14]. The use of propylphosphonic anhydride (T3P), as acid activator, for the direct conversion of carboxylic acids 14 into acyl azides **8** was reported by Basavaprabhu and his group in 2010[15]. Due to the vast advantages and broad range applications of peptide coupling agents in synthetic organic chemistry, Sureshbabu and co-workers, in 2010, firstly employed peptide coupling agents, EDC and HBTU for the preparation of acyl azides **8** from a variety of carboxylic acids 14[16].

A very simple and effective one step method was proposed by Akhlaghinia and Saadabad, in 2013, for the direct conversion of carboxylic acids **14** to the corresponding acyl azides **8** in 69-98% yields by using

triphenylphosphine-trichloroisocyanuric acid which is a safe, cheap, general and mixed reagent system17. In 2014, Pulle and co-workers synthesized acyl azides by the coupling reaction of carboxylic acids and NaN3 catalyzed by phosphonitrilic chloride trimer ($C_{16}N_3P_3$) in the presence of NMM[18]. Activation of PNT by NMM gave morpholinium salt which was treated with variety of carboxylic acids **14** to produce activated esters. Treatment of activated esters with NaN_3 produced acyl azides **8** (Scheme 5).

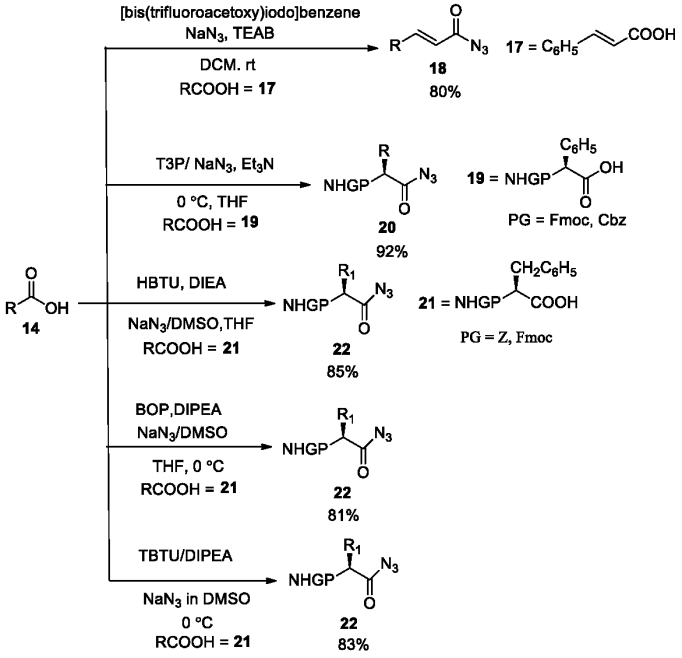


Scheme 5. *Synthesis of acyl azides from carboxylic acids using different methodologies.*

A report, involving the first use of hypervalent iodine reagents for the synthesis of acyl azides, was published by Telvekar and his group, in 2009. They converted aromatic and aliphatic α,β-unsaturated carboxylic acids **17** directly into acyl azides **18**[19]. Basavaprabhu and his group in 2010 applied their methodology of using propylphosphonic anhydride (T3P) to the synthesis of N^{α}-Fmoc and Z-protected amino acid azides **20** using N^{α}-protected amino acids **19**[15].

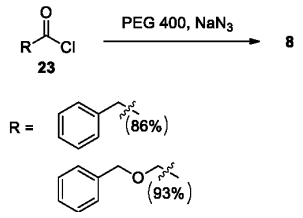
After successful conversion of carboxylic acids to acyl azides using EDC, Sureshbabu and co-workers, in 2010, employed other coupling reagents as well. For example, HBTU was employed for the formation of acyl azides **22** successfully[16]. Same group, later in 2010, utilized peptide coupling agent benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate (BOP) for transformation of a variety of carboxylic acids **21** to acyl azides **22** via a simple and straightforward strategy[20]. The methodology was also applied to the synthesis of N^{α}-Fmoc/Boc/Z protected amino acid azides which depicted the scope of the method.

Owing to the valuable applications of peptide coupling agents to the preparation of peptides and peptidomimetics, Naik and co-workers, in 2011, described applications of peptide coupling agent such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) for the preparation of acid azides **22** as well as pure urethane protected amino acid azides from carboxylic acids in high yields[21]. After the successful preparation of Fmoc-α-amino acid azides from mixed anhydrides and acid chlorides, Naik's group converted carboxylic acids to acyl azides by the application of TBTU (Scheme 6).



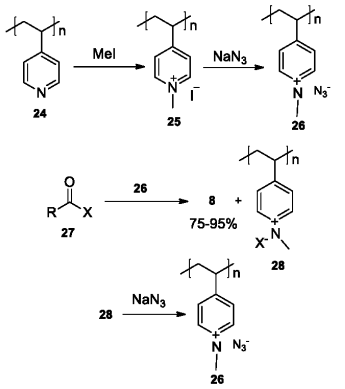
Scheme 6. *Preparation of acid azides from different carboxylic acid using different reaction conditions.*

In order to develop "Green Protocol" for the synthesis of acyl azides, Zeng et al in 2011, introduced polyethylene glycol 400 (PEG 400) as an effective green reaction medium such as for the synthesis of acyl azides **8** by nucleophilic substitution reaction of acid chlorides **23** with sodium azide at room temperature (Scheme 7) [22].



Scheme 7. *Synthesis of acyl azides **8** using polyethylene glycol 400.*

Zarchi and Barani, in 2013, employed the use of cross-linked poly(N-methyl-4-vinylpyridinium) azide ion, $[P_4\text{-VP}]N_3$ as polymeric reagent under heterogeneous environment to produce acyl azides **8** from acyl halides **27** at room temperature[23]. Cross-linked poly(N-methyl-4-vinylpyridinium) azide ion 26 was prepared from reaction of compound **24** with MeI followed by the reaction of **25** with NaN_3. Addition of **26** to acyl halide **27** yielded acyl azide **8**. $[P_4\text{-VP}]N_3$ **26** could be regenerated by treating compound **28** with NaN_3 (Scheme 8).

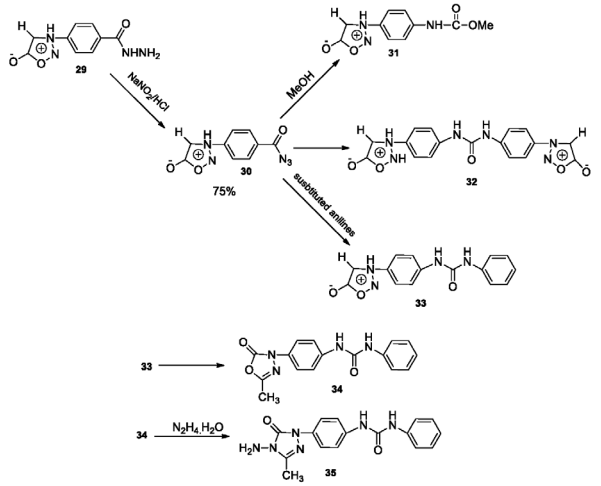


Scheme 8. *Synthesis of acyl azides from acyl halides 26 using polymeric reagent.*

Synthetic Applications of Acyl Azides

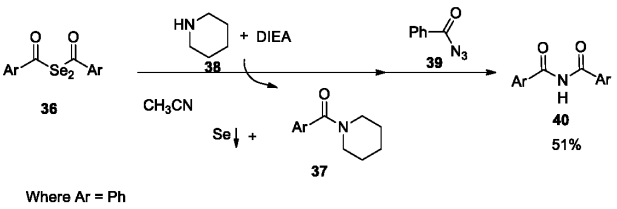
Formation of Amides, Urea derivatives, Carbamates and Urethanes

Acyl azides have found numerous applications towards the synthesis of amides, urea derivatives, carbamates and urethanes etc. In 2006, Latthe converted acyl azide **30** to carbamate **31** and urea derivatives **32**-**35** via Curtius rearrangement[24]. Acyl azide derivative 30 was formed by nitrosation of 3-(4 hydrazinocarbonyl)phenylsydnone **29** and underwent Curtius rearrangement in different boiling alcohols such as MeOH to give corresponding carbamate **31**. 3-(4-Azidocarbonyl)phenylsydnone **30** was converted to urea 4,4'-(sydnone-3-yl) diphenyl urea **32** via Curtius rearrangement. In another reaction, 3-(4-azidocarbonyl) phenylsydnone 30 underwent Curtius rearrangement when treated with different aromatic amines to produce corresponding *N*-aryl-*N'*-[4-(sydnon-3-yl)phenyl] ureas **33.** Further, compound **33** was converted to N-aryl-N'-[4-(5-methyl-1,3,4-oxadiazolin-2-one-3yl) phenyl]urea **34** by treating with bromine in acetic anhydride. In the next reaction, compound **34** was treated with hydrazine hydrate to yield N-aryl-N'-[4-(4-amino-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one-2yl)] phenyl ureas **35** (Scheme 9).



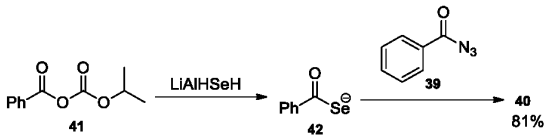
Scheme 9. *Synthesis of acyl azide derivatives **31-35** via Curtius rearrangement.*

In the same year, Surabhi prepared amides by the reaction of trialkyl ammonium selenocarboxylate with azides25. Dibenzoyl diselenide **36** was allowed to react with diisopropylethylamine (DIEA) and piperidine **38** under inert atmosphere to produce the stable N-benzoylpiperidine **37**, the selenium metal and diisopropylethylammonium benzeneselenocarboxylate which was reacted in situ with benzoyl azide **39** to give amide product **40** (Scheme 10).



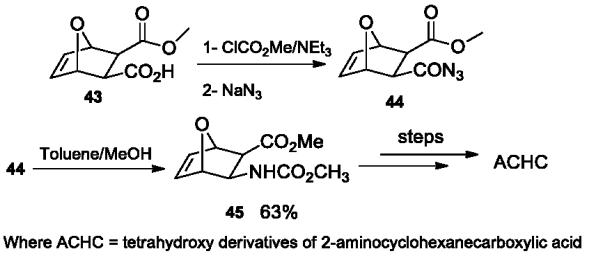
Scheme 10. *Preparation of amides* **40** *from acyl azides.*

Wu and Hu in 2007, employed the use of selenocarboxylates for the chemoselective amidation of carboxylic acids and azides26. The mixed anhydride of carboxylic acid **41** was treated with LiAlHSeH in tetrahydrofuran under nitrogen atmosphere to furnish in situ selenocarboxylate **42** with the evolution of carbon dioxide. Selenocarboxylate **42** was treated with benzoyl azide **39** to yield amide **40** in good yield (Scheme 11).



Scheme 11. *Use of selenocarboxylates for the amidation of acyl azide* **39.**

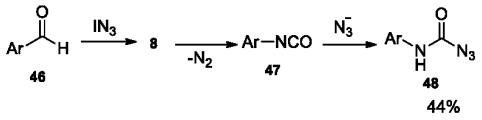
The stereoselective synthesis of tetrahydroxy derivatives of 2-amino cyclohexane carboxylic acid (ACHC) via the intermediacy of Curtius rearrangement was reported by Chola and Masesane in 200827. During the course of their methodology, half ester **43** was converted to acyl azide **44** by using methyl chloroformate which activated the free acid **43** followed by subsequent treatment with NaN3 to give acyl azide 44. Compound **44** furnished carbamate **45** by the reaction with toluene and methanol (Scheme 12). Further the carbamate **45** underwent subsequent reactions to achieve the synthesis of ACHC.



Scheme 12. *Synthesis of ACHC from acyl azide* **44**.

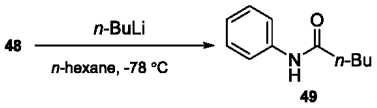
Brandt and Wirth, in 2009, converted aromatic aldehydes **46** into carbamoyl azides **48** and then,

into amides upon treatment with n-BuLi [28]. Their methodology involved continuous flow reaction conditions in microreactors (Scheme 13).



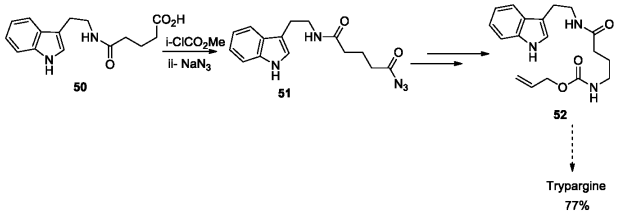
Scheme 13. *Conversion of aromatic aldehydes 46 to carbamoyl azides* **48**.

The reactivity of carbamoyl azide was found similar to isocyanates as quantitative formation of amide **49** was observed when carbmoyl azide **48** was reacted with n-BuLi (Scheme 14).



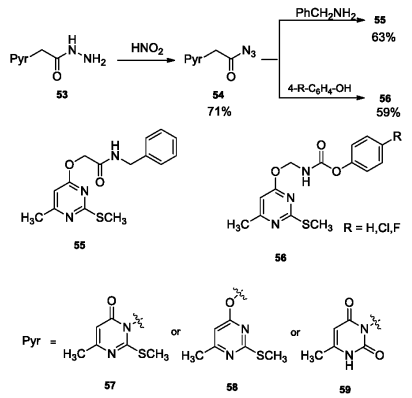
Scheme 14. *Formation of amide* **49** *from carbamoyl azide* **48**.

The asymmetric synthesis of (+)- and (-)-trypargine was reported by Pilli and Rodrigues Jr. in 200929. During the course of the synthesis, tryptamine derivative was prepared from acyl azide **51** which was obtained from corresponding carboxylic acid **50** followed by Curtius rearrangement to form compound **52** (Scheme 15).



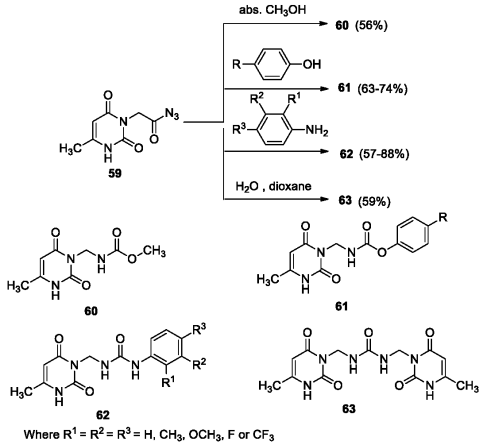
Scheme 15. *Asymmetric synthesis of (+)- and (-)-trypargine from acyl azide* **51**.

In 2010, Jakubkiene and co-workers prepared acyl azides **54** from nitrosation of hydrazides **53** [30]. Acyl azide **54** upon treatment with benzyl amine was converted to form corresponding amide **55** and carbamate **56** was formed when treated with substituted phenols via Curtius rearrangement (Scheme 16).



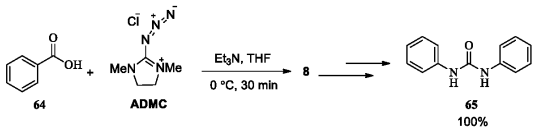
Scheme 16. *Formation of amide* **55** *and carbamate* **56** *from acyl azide* **54**.

They could convert acyl azide **59** to carbamate (**60** and **61**) and urea derivatives (**62** and **63**) upon treatment with MeOH, phenols, anilines and water respectively in good yields (Scheme 17).



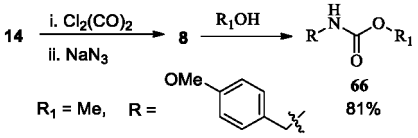
Scheme 17. *Conversion of acyl azide* **59** *to carbamateand urea derivatives.*

Kitamura and co-workers, in 2010, employed the use of 2-azido-1,3-dimethylimidazolinium chloride (ADMC) as diazotransfer reagent for the straightforward and direct preparation of various acyl azides from carboxylic acids and converted the acyl azide into urea derivative **65** (Scheme 18)31.



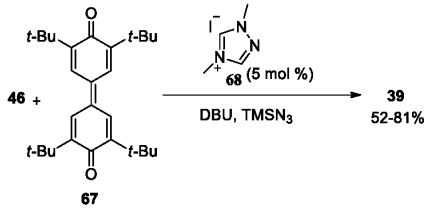
Scheme 18. *Preparation of amide 65.*

Leathen and Peterson, in 2010, reported a novel approach to achieve a variety of acyl azides from phenyl and heteroaryl acetic acids via Curtius rearrangement**32**. In this methodology, first carboxylic acid 14 was treated with oxalyl chloride followed by treatment with sodium azide to form acyl azide 8. The acyl azide 8 was captured with methanol to attain the corresponding carbamate **66** (Scheme 19).



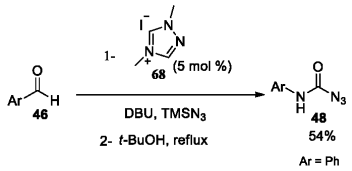
Scheme 19. *Synthesis of acyl azide and its conversion to corresponding carbamate* **66**.

Sarkar and Studer, in 2010, converted various aldehydes directly to acyl azides in reasonable to good yields by using oxidation conditions[33]. They optimized reaction conditions by choosing benzaldehyde 46 as test substrate and treated it with three different azide donors to form benzoyl azide **39** (Scheme 20).



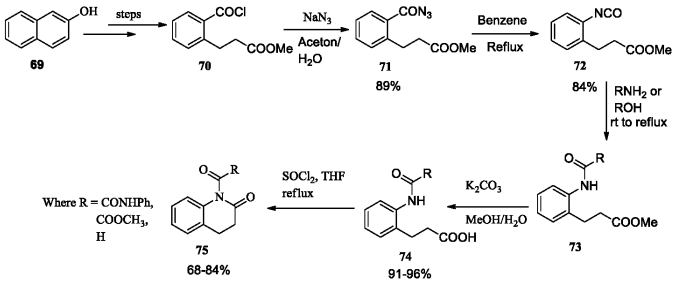
Scheme 20. *Preparation of* **39**.

They converted aldehyde **46** to corresponding phenyl carbamoyl azide **48** through Curtius rearrangement (Scheme 21).



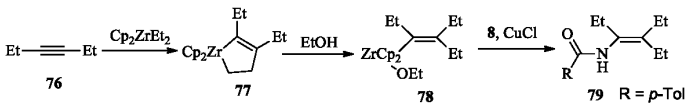
Scheme 21. *Synthesis of phenyl carbamoyl azide 48 through Curtius rearrangement.*

The 3,4-dihydroquinolin-2-one skeleton is a significant functionality in many compounds of biological and pharmaceutical importance. In 2013, Dengiz and Balci described a new pathway for the formation of 3,4-dihydroquinolin-2-one skeleton **75** via Curtius rearrangement of acyl azide **71** synthesized from 2-(2-carboxyethyl)benzoic acid (Scheme 22) [34].



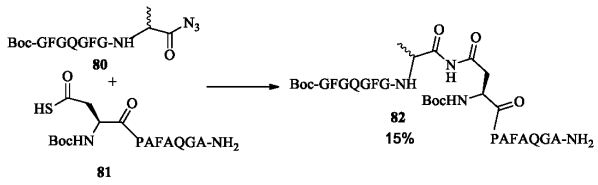
Scheme 22. *Synthesis of 3,4-dihydroquinolin-2-one derivative* **75** *from acyl azide* **71**.

Enamides are valuable in organic preparations as these give nitrogen-based functionalities into organic molecules. In 2013, Liu et al reported the described Cu-mediated amidation of alkenylzirconocenes 78, synthesized by the ethanolysis of diethylzirconacyclopentene **77** by 3-hexyne **76**, with acyl azides 8 in a one pot-reaction to yield a variety of enamides **79** under mild reaction conditions (Scheme 23)[35].



Scheme 23. *Preparation of enamides* **79** *using acyl azides.*

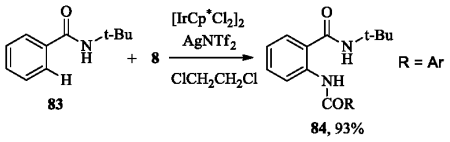
In 2013, Mhidia and co-workers described imide ligation as a capture step by reacting thioacid **81** and acyl azide **80** in the reaction of peptide bond formation (Scheme 24)[36].



Scheme 24. *Imide ligation by reacting thioacid* **81** *and acyl azide* **80**.

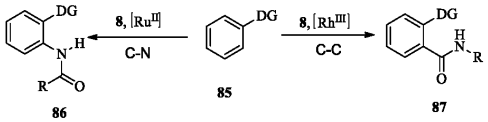
In 2013, More et al synthesized thermoplastic polyurethanes from di-isocyanates based on novel fatty acids. Their methodology involved the synthesis of fatty acid based acyl azides from corresponding hydrazides37.

In 2013, Ryu and co-workers developed a new environmental friendly method using acyl azides as nitrogen source for amidation of alkenes and arenes catalyzed by Ir(III) complex under mild reaction conditions[38]. Acyl azide 8, as internal oxidant, was used to react with benzamide **83** in the presence of iridium catalyst and silver additive giving C-H amidated product **84** in fair yield (Scheme 25).



Scheme 25. *Amidation of arenes using acyl azide 8.*

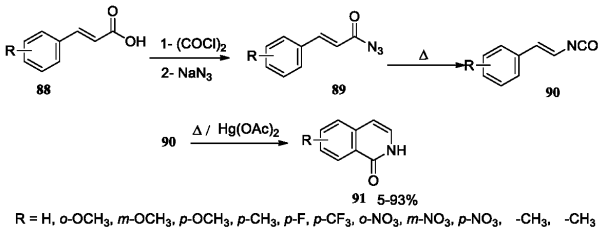
A broad range of acyl azides and arenes with diversity of functional groups were used to form amides in good yields successfully with no Curtius rearrangement. Shin et al, in 2014, explored the dual reactivity of acyl azides and used that for selective amidation (C-C or C-N) using suitable catalysts (Scheme 26) [39].



Scheme 26. *Selective C-C or C-N amidation of 85 using [RuII] and [RhIII].*

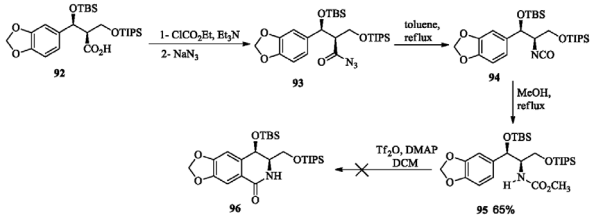
Synthesis of Heterocycles

Chuang and Wu, in 2006, employed cinnamoyl azides bearing a variety of substituents for the synthesis of substituted isoquinolinones **91** in low to good yields (Scheme 27)[40].



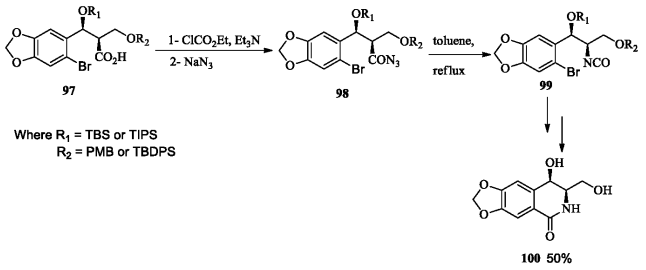
Scheme 27. *Synthesis of substituted isoquinolinones 91 from cinnamoylazides.*

Lopes and Coelho, in 2007, used acyl azides for preparing carbon skeleton constituting the structure of important alkaloids obtained from plants of the Amaryllidaceae family41. During the course of the synthesis, acid **92** was converted to acyl azide **93** using ethyl chloroformate followed by treatment with sodium azide. Isocyanate **94** was produced via Curtius rearrangement. Reaction of isocyanate **94** with methanol gave carbamate **95** which was subjected to various Bischler-Napieralski experimental procedures but the desired product **96** could not be obtained (Scheme 28).



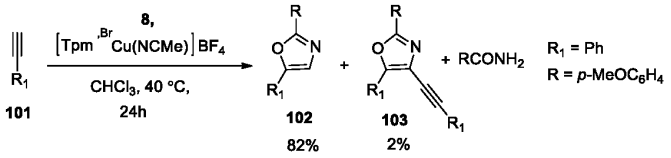
Scheme 28. *Use of acyl azides for preparation of* **95.**

They changed their synthetic strategy and synthesis of functionalized dihydroisoquinolinone **100** was accomplished by alternative pathway using acyl azide during the course of their synthesis (Scheme 29).



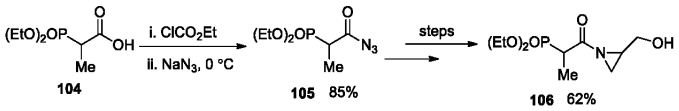
Scheme 29. *Synthesis of functionalized dihydroisoquinolinone 100 via acyl azide pathway.*

Cano et al in 2011, described a new method for the regioselective preparation of 2,5-disubstituted oxazoles **102** and **103** from acyl azides and 1-alkynes **101** using Cu (I) catalyst [Tpm*, BrCu(NCMe)] BF4 [Tpm*,Br)=tris(3,5-dimethyl-4-bromopyrazolyl) methane] (Scheme 30)[42].



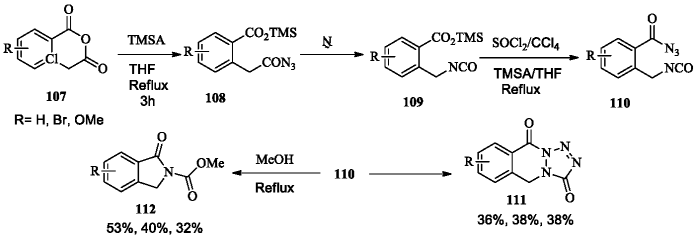
Scheme 30. *Regioselective synthesis of 2,5-disubstituted oxazoles 102 and 103 from acyl azides and 1-alkynes.*

In 2011, Keniche and co-workers synthesized aziridine, an important class of biological active compounds, through the formation of acyl azide43. During the course of their study, they employed the use of acyl azide 105 from corresponding carboxylic acid **104**. The acyl azide **105** was converted over few steps to desired aziridine **106** (Scheme 31).



Scheme 31. *Synthesis of aziridine* **106** *from acyl azide* **105**.

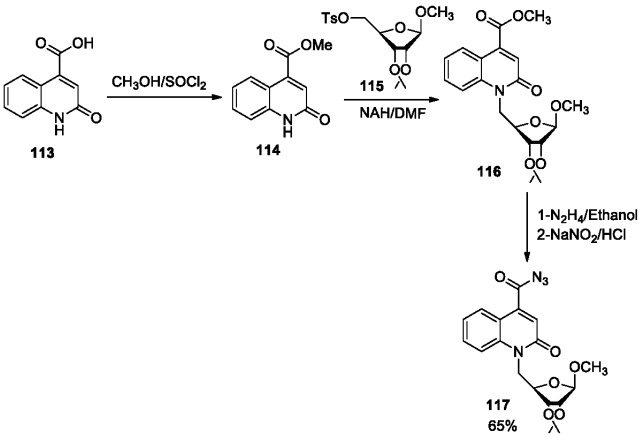
The 1- and 4-substituted tetrazolone derivatives have attracted attention due to their valuable herbicidal activity. In 2013, Ozcan and co-workers synthesized tetrazolone derivatives **111** and isoindolinones **112** from anhydrides via the formation of acyl azide **110** intermediate in a mild, simple and one-pot protocol (Scheme 32) [44].



Scheme 32. *Synthesis of tetrazolone derivatives* **111** *and isoindolinones* **112**.

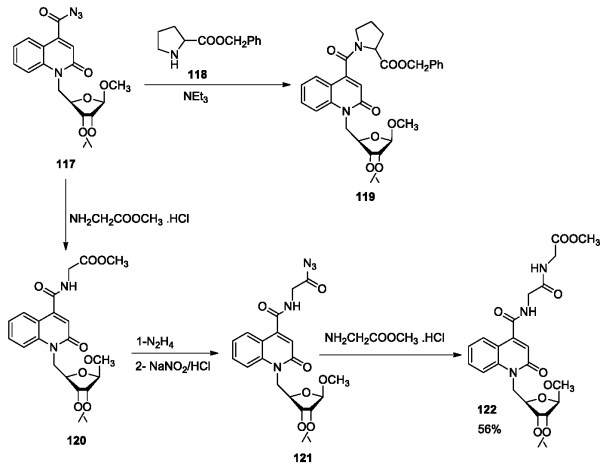
Formations of Amino Acids / Peptides

Acyl azide coupling procedure was used by Ali in 2008, to synthesize many chemotherapeutically important quinoline based nucleosides containing an amino acid ester residue at position 4 in good yield45. Quinoline 114 obtained by methyl esterification of quinoline **113** was reacted with protected ribose tosylate **115** in the presence of sodium hydride to yield **116**. Treatment of the ester **116** with hydrazine hydrate afforded hydrazide which was reacted with sodium nitrite and hydrochloric acid mixture to yield acyl azide **117** (Scheme 33).



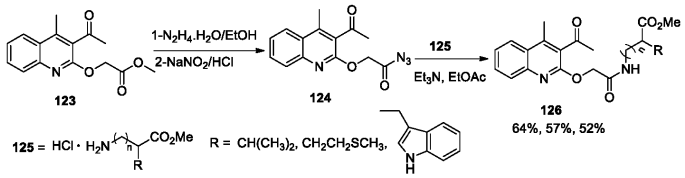
Scheme 33. *Synthesis of acyl azide* **117** *by nitrosation of hydrazide.*

Reaction of acyl azide **117** with amino acid ester **118** resulted in amino acid derivative **119**. Their group applied this methodology to the synthesis of dipeptide based quinoline derivatives **122** (Scheme 34).



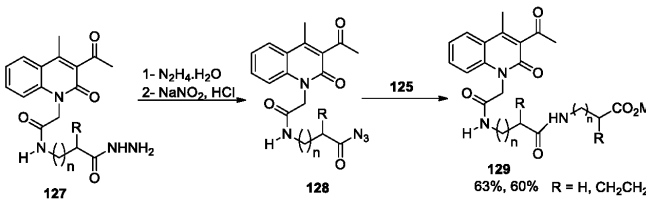
Scheme 34. *Synthesis of amino acid derivative and dipeptide based quinoline derivatives from acyl azide* **117.**

In the same year, Ali and his co-workers prepared a series of quinoline derivatives connected with a series of amino acid and dipeptides as pLT antagonists46. The ester **123** was subjected to hydrazinolysis and subsequent treatment with sodium nitrite and hydrochloric acid yielded acyl azide **124**. Different amino acid ester derivatives such as **125** were allowed to react with acyl azide to yield different 2-substituted quinoline derivatives based on amino acid esters **126** (Scheme 35).



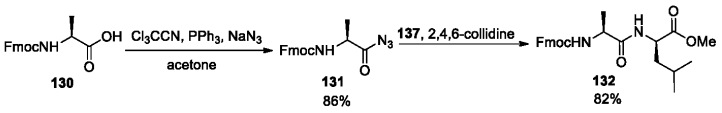
Scheme 35. *Synthesis of 2- substituted quinoline derivatives126 from acyl azide* **124**.

The methodology was further extended towards the synthesis of N-substituted dipeptide derivatives **129** (Scheme 36).



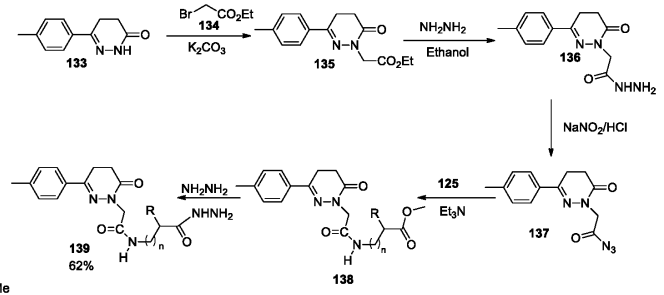
Scheme 36. *Synthesis of N-substituted didpetide derivatives* **129** *through acyl azide pathway.*

Kim and Jang described a simple, mild and effective method for the synthesis of acyl azides **131** in high yield from carboxylic acids **130** without involving Curtius rearrangement using trichloroacetonitrile, triphenylphosphine and NaN3 in 200847. The methodology was extended towards the synthesis of different dipeptides **132** (Scheme 37).



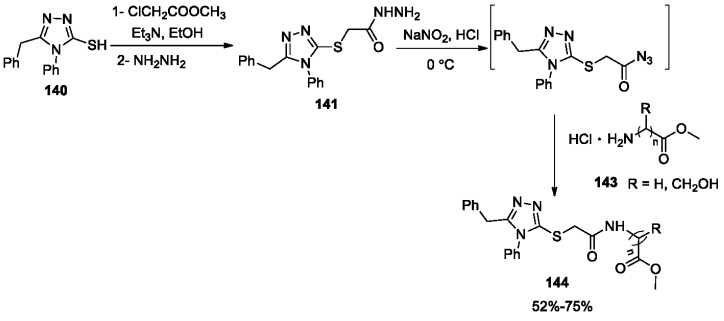
Scheme 37. Synthesis of dipeptides **132.**

Acyl azide pathway was used by El Rayes in 2008 for the preparation of a new series of dihydro-2H-pyridazin-3-one derivatives attached to N-terminal dipeptides and amino acids through acyl azide pathway48. Biologically active heterocyclic motif **133** was used to yield hydrazide **136** via N-alkylation with ethyl bromoacetate 134 followed by the reaction with hydrazine hydrate in ethanol. Hydrazide **136** underwent nitrosation to produce in situ acyl azide **137** which was treated with amino acid methyl ester hydrochloride **125** to yield **138** in good yield. Amino acid derivative **138** was further utilized for the synthesis of dipeptides **139** (Scheme 38).



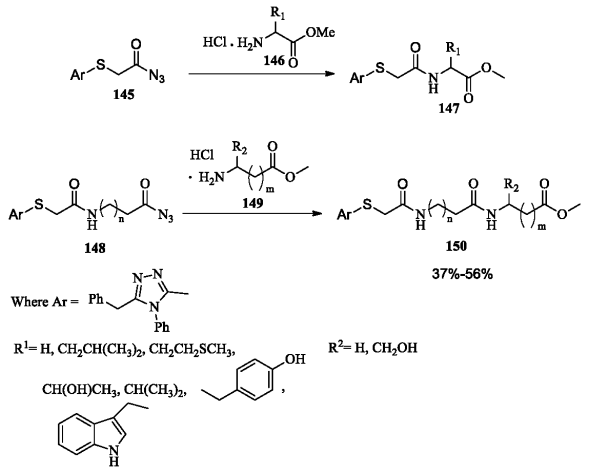
Scheme 38. *Synthesis of* **139** *through acyl azide pathway.*

Same group, in the same year, reported the synthesis of benzanilide derivatives bearing amino acids via acyl azide coupling rout[49]. In 2010, El Rayes reported one pot preparation of amino acids **144**, coupled with triazoles, via acyl azide pathway (Scheme 39)[50].



Scheme 39. *Synthesis of amino acids coupled with triazoles 144 via acyl azide pathway.*

Typically, they treated acyl azide **145** and **148** with amino acid esters **146** and **149** to yield mono peptide esters **147** and dipeptide esters **150** in good yields (Scheme 40).

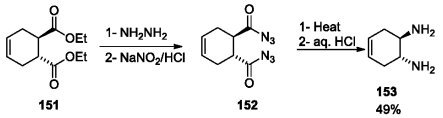


Scheme 40. *Synthesis of mono peptide esters and dipeptide esters via acyl azide procedure.*

Similar pathway was adopted by Salem and co-workers, for the synthesis of benzothiazolyl thioacetyl amino acid and peptide derivatives in high yield[51].

Miscellaneous Reactions

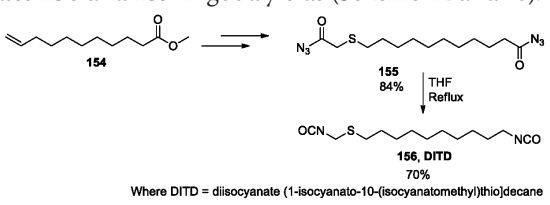
In 2012, Sprecher et al demonstrated the preparation of acyl azide and its degradation to amine using a flow apparatus attached with an automated extraction unit52. Diester **151** was converted to dihydrazide in multi-100 g quantities in batch mode which upon treatment with aq. hydrochloric acid and sodium nitrite yielded diacylazide **152**. Double Curtius rearrangement of diacylazide **152** at 100 °C produced diisocyanate which was transformed directly to diamine **153** in moderate yield using HCl (aq) (Scheme 41).



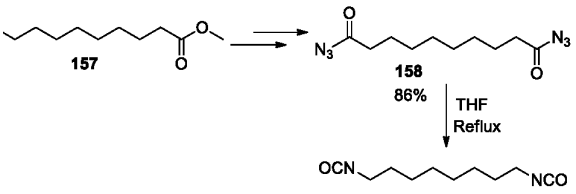
Scheme 41. *Synthesis of acyl azide and its degradation to amine* **153.**

Polyurethanes (PU), a valuable class of polymeric materials, are prepared from treatment of diisocyanates with polyols. More et al in 2013, brought about transformation of fatty acid derivatives to diisocyanates via an environmental friendly and non-phosgene protocol53. Diisocyanates were further used as comonomers to synthesize stable bio-based PU.

Diacylazides **155** and **158** were synthesized over a series of steps from ester **154** and diester **157.** Acyl azides **155** and **158** were further subjected to Curtius rearrangement in anhydrous tetrahydrofuran to yield diisocyanates **156** and **159** in good yields (Scheme 42 and 43).



Scheme 42. *Synthesis of DITD* **156**.



Scheme 43. *Synthesis of diisocyanate* **159**.

CONCLUSIONS AND FUTURE PERSPECTIVES:

Due to such vast utility of acyl azides, the development of efficient routes for their synthesis is important. This study highlights many single-step and multistep protocols developed for the synthesis of acyl azides and their extensive applications in the synthesis of amides, nitriles, cycloaddition reactions, peptide bond formation and in heterocyclic chemistry. Further, in spite of all the investigations being done on consecutive reactions of acyl azides, there is still reasonable gap to fill in terms of its applications towards heterocyclic compounds and peptides based biologically important molecules.

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