

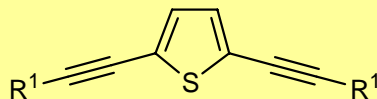
***Science of Synthesis* Worked Examples**

Practical examples of the use of *Science of Synthesis*
in resolving organic synthesis problems

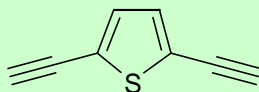
Example I The Synthesis of 2,5-Dialkynylthiophenes

Example II The Synthesis of 4-Phenylquinazoline-2-carboxylic Acid Derivatives

Example I The Synthesis of 2,5-Dialkynylthiophenes



Carry out a **Substructure Search** in *Science of Synthesis* for:

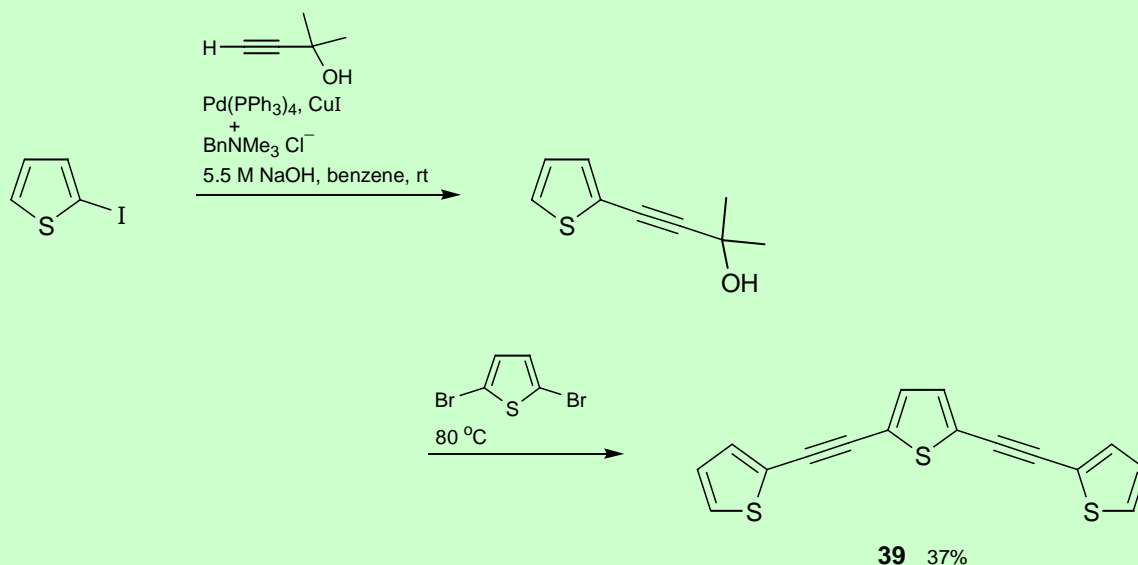


The **Hitlist** will include the following results:

- **Science of Synthesis, Vol. 3, 412**
- **Science of Synthesis, Vol. 5, 383**
- **Science of Synthesis, Vol. 6, 1282**

a) Select **hit Science of Synthesis, Vol. 3, 412**, to download the full text. You should see the following reaction, which appears surrounded by a yellow box i.e. it is marked up as a hit. You will see that this is a substitution reaction.

Scheme 146 Synthesis of 2,5-Bis(2-thienylethynyl)thiophene from 2-Methylbut-3-yn-2-ol, Tetrakis(triphenylphosphine)palladium(0), and Copper(I) Iodide in the Presence of Benzyltrimethylammonium Chloride in Benzene/Aqueous Sodium Hydroxide^[740]

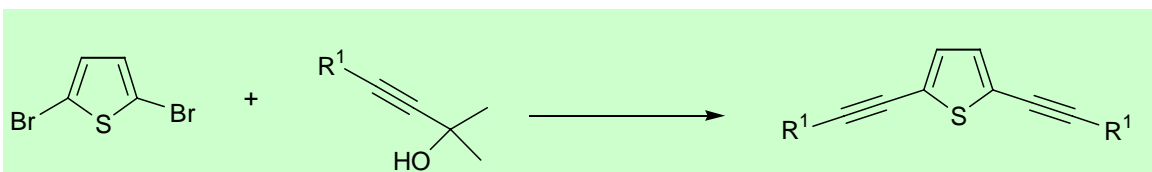


2,5-Bis(2-thienylethynyl)thiophene (39); Typical Procedure.^[740]

A mixture of 2-iodothiophene (7.16 g, 34 mmol) and 2-methylbut-3-yn-2-ol (2.86 g, 34 mmol) in benzene (**CAUTION: carcinogen**) (24 mL) was purged with N₂ and added to a mixture of CuI (0.324 g, 1.7 mmol), Pd(PPh₃)₄ (1.37 g, 1.19 mmol), and BnMe₃NCl (0.24 g, 1.19 mmol) under N₂. An O₂-free soln of 5.5M NaOH (24.5 mL) was added and the mixture was stirred at rt. After 50 h, GC analysis of an aliquot showed that the first stage of the reaction was complete. A soln of 2,5-dibromothiophene (4.11 g, 17 mmol) in benzene (5 mL) was purged with N₂ and added to the mixture, which was then stirred at 70–80 °C for 50 h. A sat. aq soln of NH₄Cl (200 mL) was then added and the mixture was extracted into benzene, filtered, and concentrated to leave a solid residue. Purification by chromatography (silica gel, hexane) gave **39**; yield: 1.86 g (36%); mp 116–118 °C.

Scroll to the bottom of the document to locate the typical procedure, and click on the reference number **[740]** to view the full reference citation.

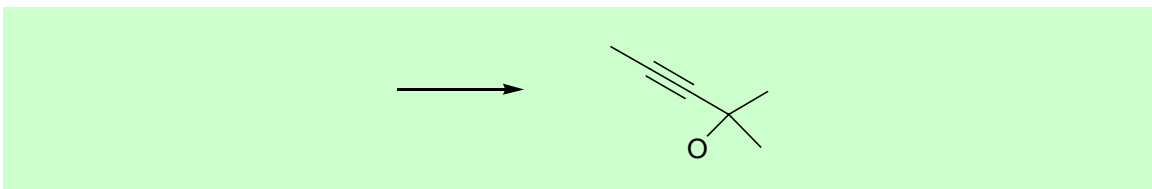
So we are basically looking at the following transformation:



The next step is to determine how to make the starting materials.

a. 1) The Preparation of the Alkynol

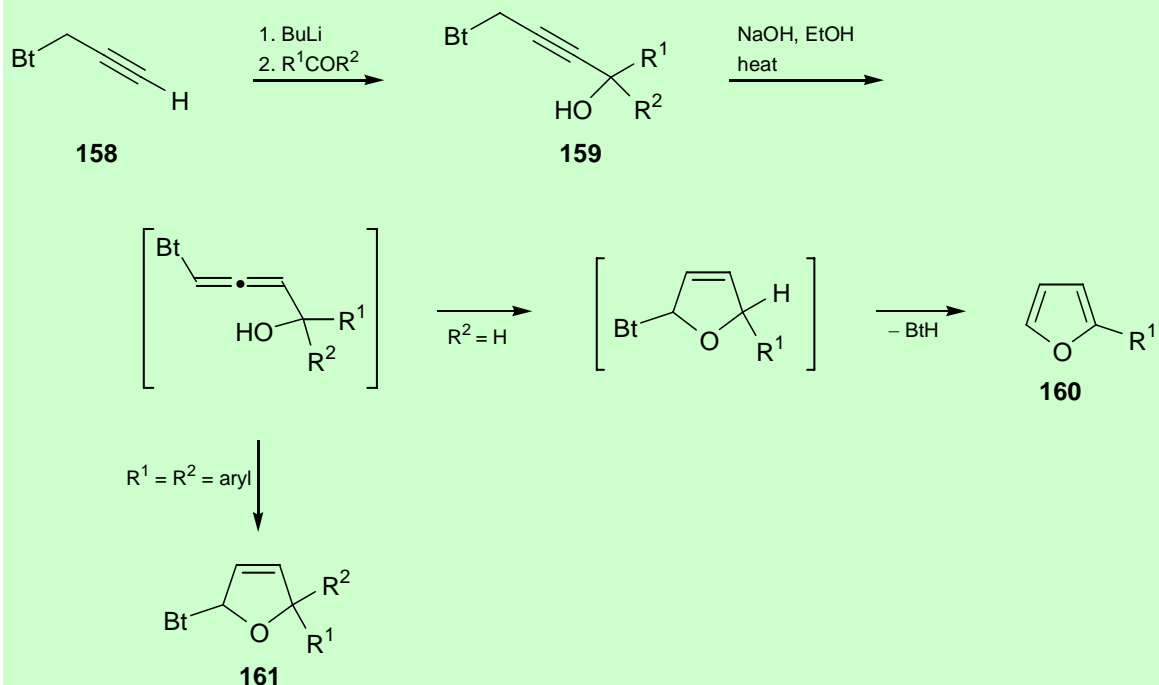
Carry out a **Reaction Search** for:



It is important to include the reaction arrow in order to define the alkynol as the product. Note, that this is by default a *substructure reaction search*.

In the **Hitlist** click on **Show Overview** to view the distribution of the hits throughout the series. Jump to the hits in Volume 9 by clicking on the [corresponding blue](#) number in the row for Volume 9. Scroll down until you locate **Science of Synthesis, Vol. 9, 216**, and click on the reaction to view the full text.

Scheme 54 Synthesis of Furans and Dihydrofurans from 1-(4-Hydroxyalkynyl)benzotriazoles^[275,276]



The first step is the one of interest i.e. the lithiation reaction and two useful references are available:

[275] Katritzky, A. R.; Li, J.; Gordeev, M. F., *J. Org. Chem.*, (1993) **58**, 3038.

[276] Katritzky, A.; Li, J., *J. Org. Chem.*, (1995) **60**, 638.

a. 2) The Preparation of the 2,5-Dibromothiophene

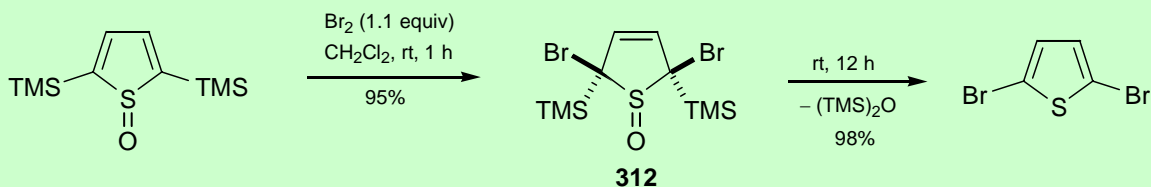
The regiospecific bromination of thiophene is not easy to achieve. Therefore you need to take the following approach:

Carry out a **Fulltext Search** for:

thiophene bromination

Select **Science of Synthesis, Vol. 9, 396.**

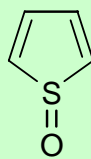
Scheme 139 Bromination of 2,5-Bis(trimethylsilyl)thiophene 1-Oxide^[1139]



The reference given for this bromination reaction is:

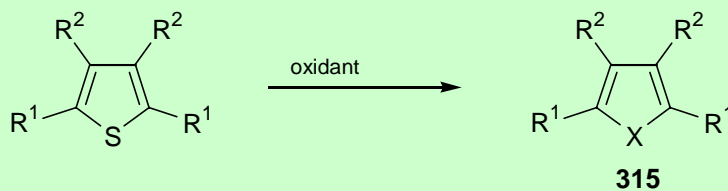
[1139] Zhang, S. Z.; Sato, S.; Horn, E.; Furukawa, N., *Heterocycles*, (1998) **48**, 227.

In order to prepare the parent thiophene *S*-oxide do a **Substructure Search** for:



Choose **Science of Synthesis, Vol. 9, 398.** You will get the following result along with a table of derivatives, a typical procedure and a number of useful references:

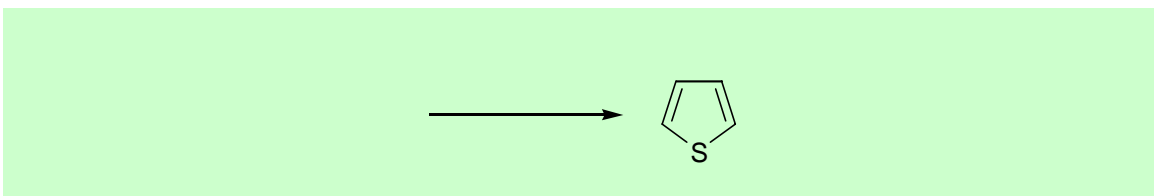
Scheme 141 Stepwise Oxidation of Thiophene to Thiophene 1-Oxides and Thiophene 1,1-Dioxides^[127,857,1116,1133,1134,1141-1143]



The synthesis of the 2,5-bis(trimethylsilyl)thiophene itself is not given but silylations in the 2-position are possible.

To find an example in Science of Synthesis:

Carry out a **Reaction Search** for thiophene:

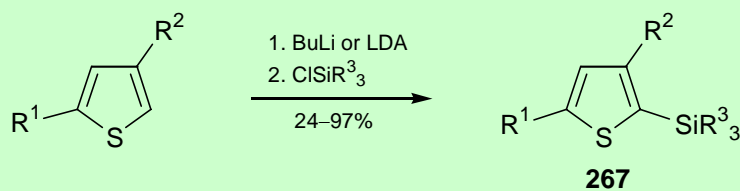


Combine with a **Fulltext Search** for:

silylation

Select **Science of Synthesis, Vol. 9, 375.** You will get the following result:

Scheme 110 2-Silylation of Thiophenes[114,942-946]



A table with a list of substituents, two procedures and a series of useful references are cited.

b) The original search for the synthesis of 2,5-dialkynylthiophenes yielded [several hits](#), one of which was **Science of Synthesis, Vol. 5, 383** (see page 2 of tutorial).

Retrieve this document by a citation search in Science of Synthesis. In the **Query** form, locate the search fields to **Search for Bibliographic Information**.

Submit a search for:

Journal/Book Title = Science of Synthesis

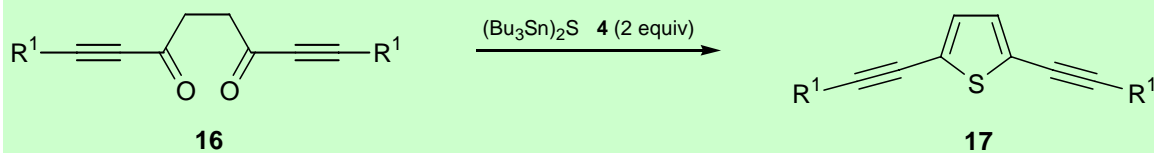
Volume = 5

Page number = 383

(Use the **Add row** command to provide additional fields)

Scroll through the full text until you identify the reaction of interest. We can see that this is a cyclization reaction.

Scheme 6 Thiophenes from Thionation of 1,4-Diketones^[30]



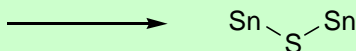
Clicking on the reference **[30]** in the scheme will take you to the following reference:

[30] Freeman, F.; Kim, D. S. H. L.; Rodriguez, E., *J. Org. Chem.*, (1992) **57**, 1722.

We now need to look at the preparation of the starting materials, in order to carry out the thionation reaction.

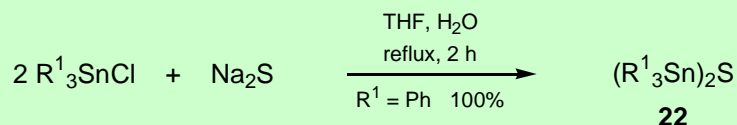
b.1.) The Preparation of a Hexasubstituted Distannathiane

Carry out a **Reaction Search** for:



It is important to include the reaction arrow in order to define the distannathiane as a product otherwise if you carry out a simple Substructure Search all the $(\text{Bu}_3\text{Sn})_2\text{S}$ reagents will be included in your answer set.

You will see [the hit](#) **Science of Synthesis, Vol. 5, 388**. Clicking on [this](#) hit downloads the full text:

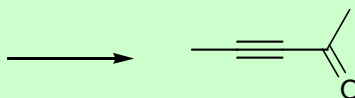
Scheme 10 Hexaphenyldistannathiane from Chlorotriphenylstannane^[10]

Hexaphenyldistannathiane (22, R¹ = Ph); Typical Procedure:^[10]

A 50-mL flask was charged with Ph₃SnCl (10.53 g, 2.73 mmol) and reagent grade THF (27 mL). A soln of Na₂S•9H₂O (6.56 g, 2.73 mmol) in H₂O (8mL) was then added in one portion, and the mixture was stirred vigorously and heated at reflux for 2 h at 65 °C (THF/H₂O 3.3:1). The progress of the reaction was followed by TLC (UV detector) and when complete THF was evaporated and EtOAc (150 mL) was added. Then the mixture was stirred for a few min to completely dissolve the Ph₆Sn₂S, which had separated. The organic phase was separated, washed with H₂O (2 x 30 mL), and dried (Na₂SO₄). The mixture was filtered and the solvent was evaporated under reduced pressure. Crude **22** (R¹ = Ph) was obtained as colorless crystals (hexanes); yield: 10.05 g (100%); mp 144–145 °C.

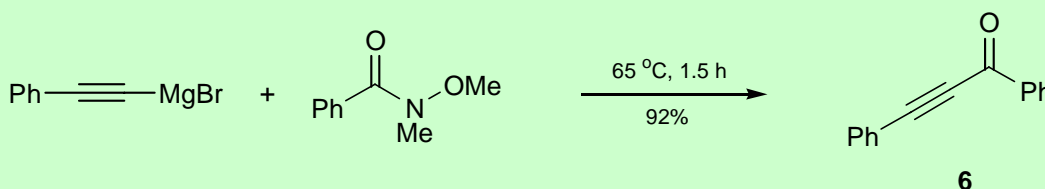
The full reference citation and links to the Houben-Weyl backfile are available in addition to the typical procedure.

b.2.) The Preparation of the Alkynone

Carry out a **Reaction Search** for:

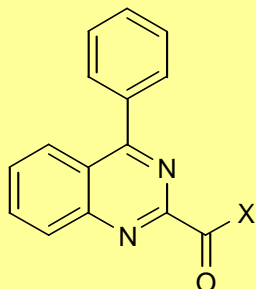


You will get [many hits spread across several volumes](#). You could try an alkylation of a succinic acid derivative thus making the diketone in one step. In the **Hitlist** click on **Show Overview** to view the distribution of the hits throughout the series. Jump to the hits in Volume 7. Scroll down until you locate **Science of Synthesis, Vol. 7, 524**, and click on the hit to view the full text.

Scheme 4 Reaction of Phenylethynylmagnesium Bromide with *N*-Methoxy-*N*-methylbenzamide^[16]


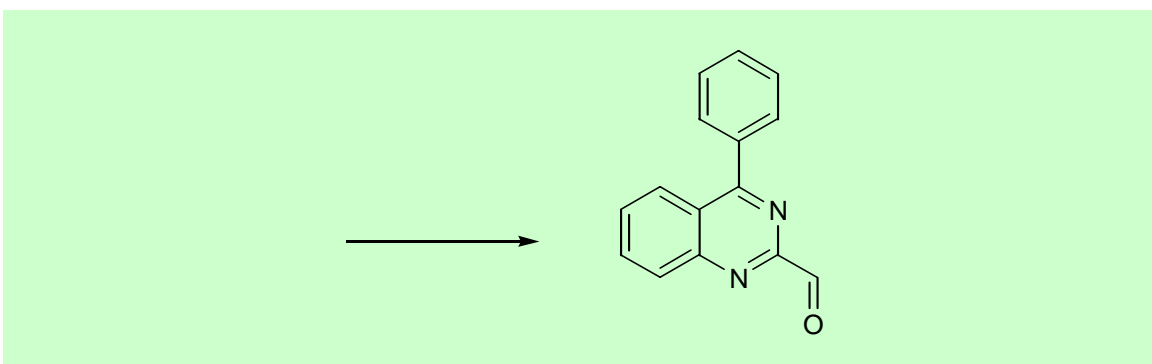
[16] Nahm, S.; Weinreb, S. M., *Tetrahedron Lett.*, (1981) **22**, 3815.

Example II Synthesis of 4-Phenylquinazoline-2-carboxylic Acid Derivatives



X=OH, OEt, NHAc, NHPH

Carry out a **Reaction Search** for:



(note that this is by default a *substructure reaction search*)

You will get [a number of hits](#).

Synthesis is possible via:

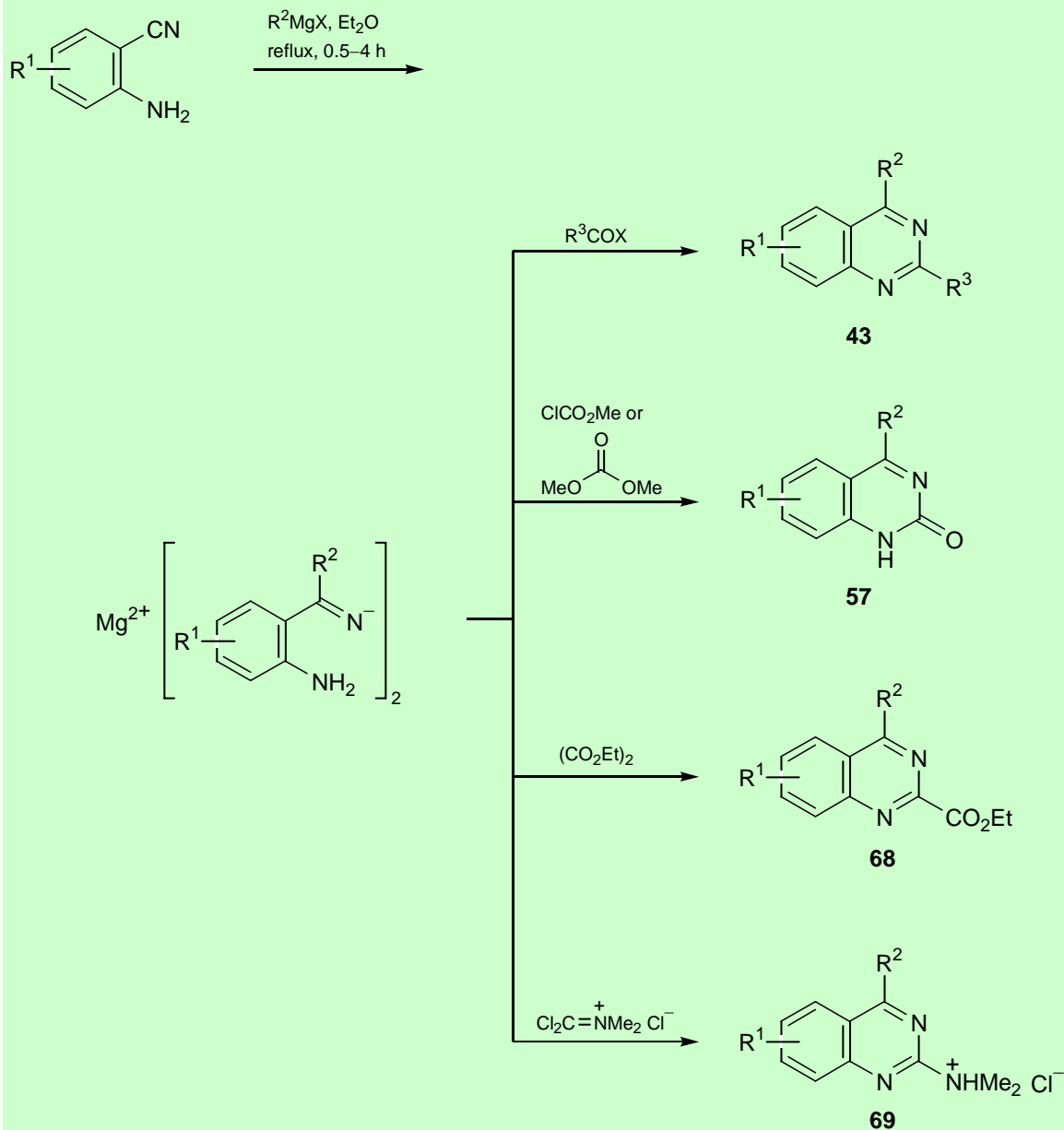
- a) The Cyclization of 2-Aminobenzonitriles (**Science of Synthesis, Vol. 16, 614**)
- b) The Cyclization of 3-Phenyl-2,1-benzosoxazole (**Science of Synthesis, Vol. 16, 655**)
- c) Ring Contraction Reactions (**Science of Synthesis, Vol. 16, 655**) and (**Science of Synthesis, Vol. 16, 669**)
- d) Elimination Reactions (**Science of Synthesis, Vol. 16, 670**)

Let us take a look at the first two of these in more detail.

a) The Cyclization of 2-Aminobenzonitriles (**Science of Synthesis, Vol. 16, 614**)

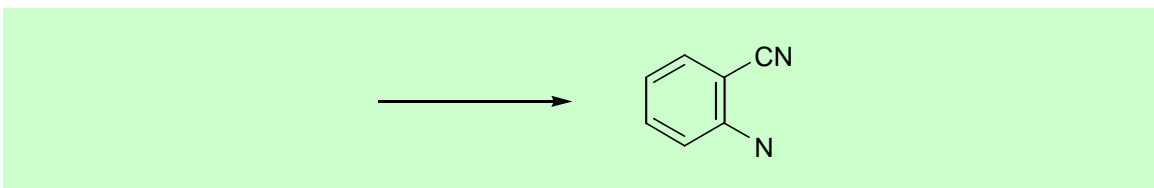
Clicking on [this hit \(Science of Synthesis, Vol. 16, 614\)](#) gives you the following information:

Scheme 49 Quinazolines from 2-Aminobenzonitriles, Grignard Reagents, and Carbonyl Compounds or Phosgene Iminium Chlorides[377,378]



The reaction of interest is the sixth reaction down in the table, with reference number [377].

To locate a preparation for the starting materials, carry out a **Reaction Search** for the substructure given below. This should yield over 25 different hits.

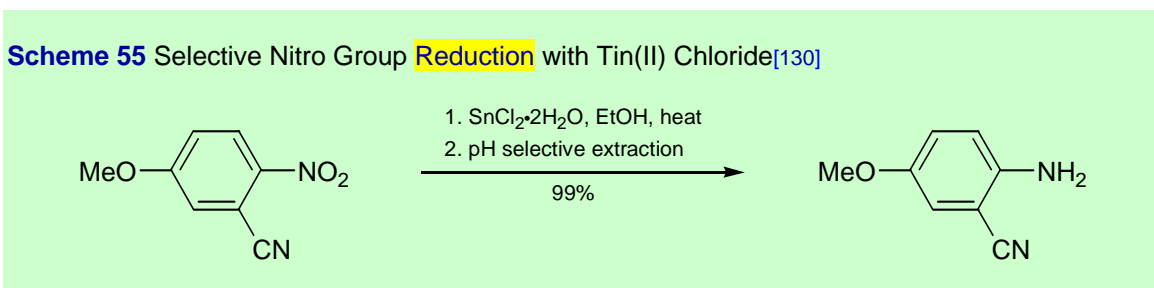


Now search using exactly the same query together with the following term in the **Fulltext** field:

reduction

In this case you get many fewer hits so you have managed to narrow down your hit list considerably.

The result of interest is Science of Synthesis, Vol. 5, 344 and the preparation of the required starting material through selective nitro group reduction with tin(II) chloride.



A reference for this type of reaction is available:

[130] Bellamy, F. D. ; Ou, K., *Tetrahedron Lett.*, (1984) **25, 839.**

b) The Cyclization of 3-Phenyl-2,1-benzisoxazole (**Science of Synthesis, Vol. 16, 655**)

We now illustrate how to retrieve one of the above hits by submitting a [bibliographic search](#). [This is done by searching for:](#)

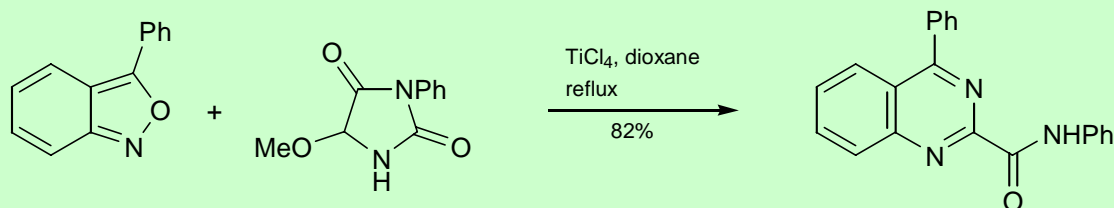
Journal/Book Title = Science of Synthesis

Volume = 16

Page number = 655

Download the full text to view:

Scheme 114 N,4-Diphenylquinazoline-2-carboxamide from 3-Phenyl-2,1-benzisoxazole^[588]



Together with the following reference:

[588] Ohta, K.; Nakamura, Y.; Iwaoka, J.; Nomura, Y., *Nippon Kagaku Kaishi*, (1990), 72; *Chem. Abstr.*, (1990) **113**, 6272.

In order to find out how to prepare the benzisoxazole you can do an **Exact Structure Search** for the 3-phenyl-2,1-benzisoxazole [that will yield several hits](#), [including:](#)

Science of Synthesis, Vol. 11, 343

Science of Synthesis, Vol. 11, 346

Science of Synthesis, Vol. 11, 348

Science of Synthesis, Vol. 11, 353

Science of Synthesis, Vol. 11, 360

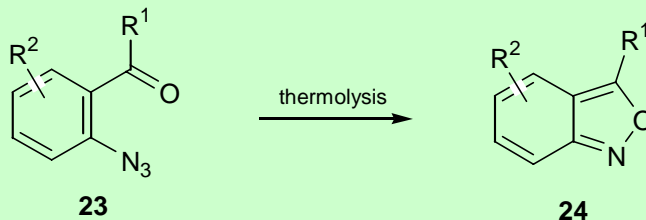
Science of Synthesis, Vol. 11, 615

Science of Synthesis, Vol. 16, 655

Science of Synthesis, Vol. 17, 771

If we just take a look at one example [e.g.](#) **Science of Synthesis, Vol. 11, 343**, we can see that the desired benzisoxazole is formed via a cyclization reaction:

Scheme 7 2,1-Benzisoxazoles by Thermolysis of 2-Azidoaryl Aldehydes and Ketones^[15,74,76,80,84,85]



A range of different possible substituents are given together with varying reaction conditions. A detailed experimental procedure for the preparation of 3-phenyl-2,1-isoxazole is given.

3-Phenyl-2,1-benzisoxazole (24, R¹ = Ph; R² = H):^[89]

A soln of 2-azidoaryl ketone **23** (R¹ = Ph; R² = H; 3.5 g, 16 mmol) in chlorobenzene (40 mL) was added dropwise over 10 min to boiling chlorobenzene (160 mL) and the resulting soln was heated under reflux for 1 h. The excess of solvent (ca. 190 mL) was removed under reduced pressure, and the residual oil was cooled and then triturated with petroleum ether (bp 40-60 °C, 50 mL) until the residue solidified. The product was collected by filtration and crystallized (50% aq EtOH) as colorless prisms; yield: 2.5-2.8 g (82-92%); mp 54 °C.

Use the Forward/Backward command to download the Hit documents in sequential order and browse through the alternative examples.

