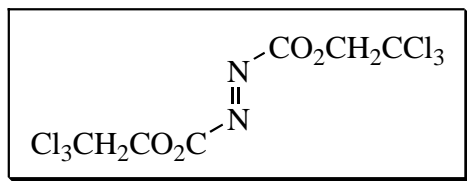


Bis(2,2,2-trichloroethyl) Azodicarboxylate



[38857-88-4]

C₆H₄Cl₆N₂O₄

(MW 380.83)

(a reactive dienophile,² diene,⁷ enophile,⁸ and aminating agent¹⁰)

Physical Data: mp 110-111 °C.

Solubility: sol in a wide range of organic solvents.

Form Supplied in: slightly yellow plates.

Analysis of Reagent Purity: ¹H NMR (CDCl₃) displays a singlet at δ 5.05.

Preparative Method: commercially available.^{1,9}

Purification: recrystallize from pentane.

Handling, Storage, and Precautions: as with all azo compounds, caution should be exercised to avoid exposure of the material to heat. Store in a brown bottle.

Amination of arenes. Bis(2,2,2-trichloroethyl) azodicarboxylate (**1**) can serve, as do other azodicarboxylates, as a source of electrophilic nitrogen. One important application provides easy access to aryl hydrazines and anilines. These product classes can be obtained by allowing aryllithium or aryl magnesium bromide reagents to react with azodicarboxylates followed by hydrolysis or N-N bond reduction. When **1** is used, because of its enhanced electron deficiency, activation of the arene is not always necessary. Catalysis with Lewis or Brønsted acid enables efficient amination of electron rich aromatic rings with **1**. For example **1** and anisole react at room temperature in the presence of catalytic ZnCl₂ to give the corresponding N,N-biscarbamate in 91% yield.¹⁰ Under identical conditions and using diethyl

azodicarboxylate only 7% of the desired product is obtained. When substituted acetophenone substrates are used, the in situ formation of indazole products is observed subsequent to N,N-biscarbamate reduction. (eq 4). One limitation of this methodology is that when para-substituted substrates are used, the reactions are slow and product mixtures are obtained. This limitation is overcome by using a Brønsted acid. Thus 1,4-dimethoxy benzene and **1** react in the presence of trifluoromethanesulfonic acid to give the corresponding N,N-biscarbamate product in 85% yield.¹¹ It should also be noted that **1** has been used to access 3-amino derivatives on indole, via Lewis acid catalysis. Para-amination of organotin phenoxides has been achieved and is catalyzed by LiClO₄ in ether as the solvent.¹²

Amination of enol ethers and enolates. It has been known for quite some time that the addition of enol ethers and enolates to azodicarboxylates can provide good yields of α -hydrazino carbonyl compounds, including carboxylic acids, and thus, of α -amino acids.¹³ When performed in an asymmetric environment, this route can be exploited for the synthesis of enantiomerically pure non-natural amino acids. One report on the amination of chiral β -keto amides of Evans' oxazolidinone with azodicarboxylates (Et, i-Pr, t-Bu, Bzl), catalyzed by Ni(II), observed modest diastereoselectivity but unfortunately did not state the diastereoselectivity observed when using **1**.¹⁴ Jørgensen and coworkers have examined the use of azodicarboxylates as electrophilic sources of nitrogen for the amination of β -keto esters and α -cyano esters to construct amino bearing quaternary chiral centers.¹⁵ In the presence of the chiral base β -isocupreidine excellent yields were observed for most of the azodicarboxylates that were used. When **1** was used, poor enantioselectivity was observed compared to other azodicarboxylates (eq 5).

Pentavalent oxaphosphonates, or phosphoenol ethers, react with azodicarboxylates at room temperature to give β -hydrazido- γ -ketophosphonates. When **1** is used, because of its enhanced reactivity, the best results are obtained by adding the oxaphospholene to **1** at $-78\text{ }^{\circ}\text{C}$ in ether (eq 6).¹⁶ It was found that it is necessary to use ZnCl_2 as catalyst for conjugated oxaphospholenes. This methodology has been exploited in studies directed toward the synthesis of phosphonate analogs of sphingomyelin and related compounds.¹⁷

Reactivity toward non-carbon nucleophiles. The reaction of azodicarboxylates with non-carbon nucleophiles has also been observed. Perhaps the most well known example is the reaction of azodicarboxylates with phosphines in the presence of acid to form the reactive intermediate for the stereoselective Mitsunobu reaction. At least one report demonstrates that the use of **1** in the Mitsunobu reaction under carefully controlled conditions can result in superior stereoselectivities. The use of triethyl methanetricarboxylate as acid and nucleophile, with trimethylphosphine and **1** in toluene solvent at $0\text{ }^{\circ}\text{C}$ led to superior stereoselectivity, compared to other azodicarboxylates, in the carbon-carbon bond forming Mitsunobu reaction leading to the synthesis of substituted cycloalkyl[*b*]indoles (eq 7).¹⁸

Sulfinic acid salts also add to **1** in order to give sulfonylhydrazides.¹⁹ Sulfinic acid salts react with **1** in a mixture of 1:1 THF and H_2O in the presence of 0.1 equivalents of TFA. It was noted however that these conditions resulted in significant decomposition of **1** and thus an excess was required. Extensive optimization efforts resulted in using THF as the solvent with 1.1 equivalents of TFA at $0\text{ }^{\circ}\text{C}$ to obtain good to excellent yields using both aryl and alkyl sulfinic acid salts. Subsequent reduction of the sulfonylhydrazides with Zn dust/AcOH/acetone provided the unsubstituted sulfonamides.

Sigmatropic and cycloaddition reactions. The azo-ene reaction of azodicarboxylates typically requires heating (80 °C in benzene). When water is used as solvent a significant rate and yield enhancement is observed at a lower temperature (50 °C).²⁰ However, when mediated with stoichiometric SnCl₄ the reaction proceeds at -60 °C.²¹ Recently a catalytic Lewis acid mediated version of the azo-ene reaction of azodicarboxylates has been developed. Diethyl azodicarboxylate undergoes an ene reaction with cyclopentene mediated by catalytic metal triflates at room temperature in poor yield after long reaction times. In contrast, excellent yields are obtained when **1** is used.²² Of the metal triflates investigated, those of Cu, Nd, Zn and Yb were determined to be effective. This methodology was further extended to an asymmetric version employing a chiral oxazoline ligand and oxazolidinone modified trichloroethyl azodicarboxylate. Poor to moderate enantiomeric excesses were achieved in both the azo-ene and Diels-Alder reactions.

The reactivity of **1** as a dienophile is excellent. The carbamate products obtained are usually converted to the hydrazide or azo compounds. The hydrazide products may undergo a retro-Diels-Alder reaction to regenerate the diene. This reactivity was incorporated into a strategy that cleverly employed **1** as a diene protecting group in the synthesis of (-)-zeylena (eq 8).²³ Azo products derived from **1** via Diels-alder reaction can be used to generate synthetically useful and theoretically interesting diradicals.^{2,4,24,25}

Carbamate cleavage methods. The inherent electrophilicity of **1** gives it an advantage over other azodicarboxylates as the examples cited above have shown. Another advantage to the use of **1** is the existence of a variety of methods for cleavage of the carbamate products in order to access amine, hydrazide, and azo compounds. Other azodicarboxylates must be hydrolyzed under strongly basic or strongly acidic conditions.

While applicable to carbamate products derived from **1**, they may also be cleaved reductively. A convenient method has been developed for this purpose which uses zinc dust in a solvent mixture of 1M aqueous $\text{KH}_2\text{PO}_4/\text{THF}$.²⁶ It is important to maintain vigorous and consistent stirring in order to achieve the requisite slurry and obtain excellent yields. This method avoids the necessity to prepare zinc/copper couple or use of acetic acid as solvent. Electrochemical reduction methods have also been developed that make use of both divided and single cell techniques.^{6,27} Other reductive methods include the use of sodium-2-thiophenetelluroate,²⁸ cadmium dust in DMF/HOAc,²⁹ and 10% Cd/Pb couple in 1M aqueous NH_4OAc .³⁰ The later method has the advantage of being quick and efficient.

9. Brown C W, Liu S, Klucik J, Berlin K D, Brennan P J, Kaur D, Benbrook D M. *J. Med Chem.* 2004; **47**: 1008-1017.
10. Mitchell H, Leblanc Y. *J. Org. Chem.* 1994; **59**: 682-687.
11. Leblanc Y, Boudreault N. *J. Org. Chem.* 1995; **60**: 4268-4271.
12. Kinart W J, Kinart C M, Tran Q T, Oszczeda R, Nazarski, R B. *Appl. Organometal. Chem.* 2004; **18**: 398-400.
13. Gennari C, Colombo L, Bertolini G. *J. Am. Chem. Soc.* 1986; **108**: 6394-6395.
14. Marchi C, Trepas E, Moreno-Manas M, Vallribera A, Molins E. *Tetrahedron* 2002; **58**: 5699-5708.
15. Saaby S, Bella M, Jørgensen K A. *J. Am. Chem. Soc.* 2004; **126**: 8120-8121.
16. McClure C K, Mishra P K, Grote C W. *J. Org. Chem.* 1997; **62**: 2437-2441.
17. McClure C K, Mishra P K, *Tetrahedron Lett.* 2002; **43**: 5249-5253.

18. Hillier M C, Marcoux J-F, Zhao D, Grabowski E J J, McKeown A E, Tillyer R D. *J. Org. Chem.* 2005; **70**: 8385-8394.
19. Chan W Y, Berthellette C. *Tetrahedron Lett.* 2002; **43**: 4537-4540.
20. Narayan S, Muldoon J, Finn M G, Fokin V V, Kolb H C, Sharpless K B. *Angew. Chem. Int. Ed.* 2005; **44**: 3275-3279.
21. Brimble M A, Heathcock C H. *J. Org. Chem.* 1993; **58**: 5261-5263.
22. Aburel P S, Zhuang W, Hazell R G, Jørgensen K A. *Org. Biomol. Chem.* 2005; **3**: 2344-2349.
23. Hudlicky T, Seoane G, Pettus T. *J. Org. Chem.* 1989; **54**: 4239-4243.
24. Carroll G L, Harrison R, Gerken J B, Little R D. *Tetrahedron Lett.* 2003; **44**: 2109-2112.
25. Maiti A, Gerken J B, Masjedizadeh M R, Mimieux Y S, Little R D. *J. Org. Chem.* 2004; **69**: 8574-8582.
26. Just G, Grozinger K. *Synthesis* 1976; 457-458.
27. Schwaebe M K, Little R D. *Electrochimica Acta* 1997; **42**: 2201-2203.
28. Lakshmikantham M V, Jackson Y A, Jones R J, O'Malley G J, Ravichandran K, Cava M P. *Tetrahedron Lett.* 1986; **27**: 4687-4688.
29. Giorgio C D, Pairet S, Schwergold C, Patino N, Condom R, Giorgio A F-D, Guedj R. *Tetrahedron* 1999; **55**: 1937-1958.
30. Dong Q, Anderson C E, Ciufolini M A. *Tetrahedron Lett.* 1995; **36**: 5681-5682.

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