

Clarke, Modet & C^o
COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 03-055750- -00011-0000

Fecha: 2007-06-01 16:01:07 Dep. 2020 NUECREACION
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SEÑORES
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

COD: 008

RE.: SOLICITUD DE PATENTE EN COLOMBIA
EXPEDIENTE N° 03-055750
TITULO: PROCESO PARA PREPARAR CLOPIDOGREL.
SOLICITANTE: CADILA HEALTHCARE LIMITED
FECHA SOLICITUD: 02 de julio de 2003

ASUNTO: CONTESTACIÓN A REQUERIMIENTO OFICIAL

DILIA RODRIGUEZ D'ALEMAN, en mi condición de apoderada de la sociedad solicitante, por el presente escrito doy respuesta a su auto notificado por estado de 23 de marzo de 2007, el cual vence el día 22 de junio de 2007, y adjunto copia del documento:

- JERRY MARCH. "Advance Organic Chemistry". 1992. WILEY& SONS, New York. XP002215119 198280. Page 812, 964, 965, 966.

Solicitado por esa Superintendencia en virtud del artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina.

Se proporciona la publicación completa, con lo cual, ese Despacho pueda proceder a realizar el análisis de la patentabilidad de la invención correspondiente a la presente solicitud.

Por lo tanto, se solicita respetuosamente a la Oficina de Patentes Colombiana continuar con el estudio de la solicitud en curso.

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Clarke, Modet & C^o
COLOMBIA

Agradezco continuar con el presente trámite.

Señor Jefe,



DILIA RODRIGUEZ D'ALEMAN

ADP/MRO/srch

P-494



Anexo: Copia del artículo solicitando.

XP-002215119

P.D. 1992
p. 012 + 964 = 4
+ 965 + 966

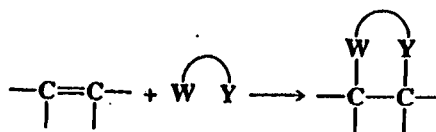
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catalyzed. When Z is COR or, more especially, CHO, 1,2 addition (6-51) is an important competing reaction and may be the only reaction. Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH₄Cl, and HCl or by Ni or Pd compounds.⁵⁸⁹ The HCN can be generated in situ from acetone cyanohydrin (see 6-49), avoiding the use of the poisonous HCN.⁵⁹⁰ One or two moles of HCN can be added to a triple bond, since the initial product is a Michael-type substrate. Acrylonitrile is commercially prepared this way, by the addition of HCN to acetylene. Alkylaluminum cyanides, e.g., Et₂AlCN, or mixtures of HCN and trialkylalanes R₃Al are especially good reagents for conjugate addition (HCN)⁵⁹¹ to α,β-unsaturated ketones and α,β-unsaturated acyl halides. HCN can be added to ordinary olefins in the presence of dicobalt octacarbonyl⁵⁹² or certain other transition-metal compounds.⁵⁹³ An indirect method for the addition of HCN to ordinary olefins uses an isocyanide RNC and Schwartz's reagent (see 5-13); this method gives anti-Markovnikov addition.⁵⁹⁴ *t*-Butyl isocyanide and TiCl₄ have been used to add HCN to C=C-Z olefins.⁵⁹⁵ OS I, 451; II, 498; III, 615; IV, 392, 393, 804; V, 239, 572; VI, 14.

For addition of ArH, see 1-12 (Friedel-Crafts alkylation).

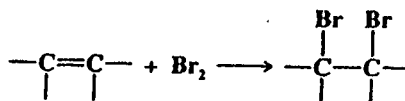
Reactions in Which Hydrogen Adds to Neither Side

Some of these reactions are *cycloadditions* (reactions 5-36, 5-37, 5-42, and 5-45 to 5-52). In such cases addition to the multiple bond closes a ring:



A. Halogen on One or Both Sides

5-26 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen) Dihalo-addition



⁵⁸⁹Jackson; Lovel *Aust. J. Chem.* 1983, 36, 1975.

⁵⁹⁰Jackson; Permuter *Chem. Br.* 1986, 338.

⁵⁹¹For a review, see Nagata; Yoshioka *Ref.* 588.

⁵⁹²Arthur; England; Pratt; Whitman *J. Am. Chem. Soc.* 1954, 76, 5364.

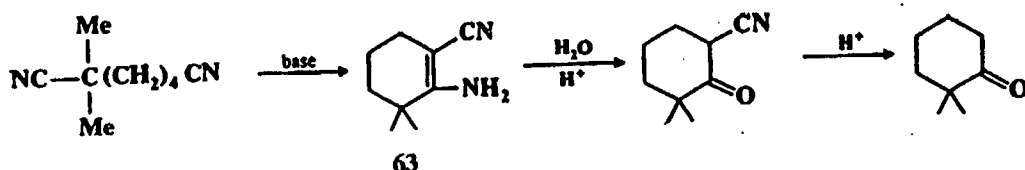
⁵⁹³For a review, see Brown, *Ref.* 588, pp. 658-667. For a review of the nickel-catalyzed process, see Tolman; McKinney; Seidel; Druliner; Stevens *Adv. Catal.* 1985, 33, 1-46. For studies of the mechanism see Tolman; Seidel; Druliner; Domaille *Organometallics* 1984, 3, 33; Druliner *Organometallics* 1984, 3, 205; Bäckvall; Andell *Organometallics* 1986, 5, 2350; McKinney; Roc *J. Am. Chem. Soc.* 1986, 108, 5167; Funabiki; Tatsami; Yoshida *J. Organomet. Chem.* 1990, 384, 199. See also Jackson; Lovel; Perlmutter; Smalridge *Aust. J. Chem.* 1988, 41, 1099.

⁵⁹⁴Buchwald; LeMaire *Tetrahedron Lett.* 1987, 28, 295.

⁵⁹⁵Ito; Kato; Imai; Saegusa *J. Am. Chem. Soc.* 1982, 104, 6449.

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course, hydrolyzable (6-2), so β -keto nitriles can be prepared in this manner. The Thorpe reaction can be done internally, in which case it is called the *Thorpe-Ziegler reaction*.⁶⁹² This is a useful method for closing large rings. Yields are high for five- to eight-membered rings, fall off to about zero for rings of nine to thirteen members, but are high again for fourteen-membered and larger rings, if high-dilution techniques are employed. The product

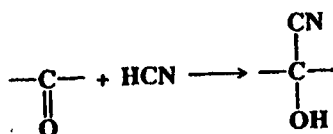


in the Thorpe-Ziegler reaction is not the imine, but the tautomeric enamine, e.g., 63; if desired this can be hydrolyzed to an α -cyano ketone (6-2), which can in turn be hydrolyzed and decarboxylated (6-5, 2-40). Other active-hydrogen compounds can also be added to nitriles.⁶⁹³

OS VI, 932.

5. Other Carbon Nucleophiles

6-49 The Formation of Cyanohydrins O-Hydro-C-cyano-addition



The addition of HCN to aldehydes or ketones produces cyanohydrins.⁶⁹⁴ This is an equilibrium reaction. For aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible, except with sterically hindered ketones such as diisopropyl ketone. However, ketones ArCOR give poor yields, and the reaction cannot be carried out with ArCOAr since the equilibrium lies too far to the left. With aromatic aldehydes the aldol condensation (6-54) competes. With α,β -unsaturated aldehydes and ketones, 1,4-addition competes (5-25). Ketones of low reactivity, such as ArCOR , can be converted to cyanohydrins by treatment with diethylaluminum cyanide Et_2AlCN (see OS VI, 307) indirectly, with cyanotrimethylsilane Me_3SiCN ⁶⁹⁵ in the presence of a Lewis acid or base,^{695a} followed by hydrolysis of the resulting O-trimethylsilyl cyanohydrin 64. When TiCl_4 is used,

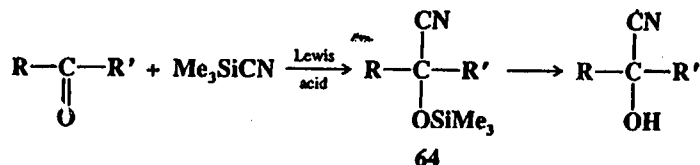
⁶⁹²For a monograph, see Taylor; McKillop *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*; Wiley: New York, 1970. For a review, see Schaefer; Bloomfield, *Org. React.* 1967, 15, 1-203.

⁶⁹³See for example, Josey *J. Org. Chem.* 1964, 29, 707; Barluenga; Fustero; Rubio; Gotor *Synthesis* 1977, 780; Hiyama; Kobayashi *Tetrahedron Lett.* 1982, 23, 1597; Gewald; Bellmann; Jansch *Liebigs Ann. Chem.* 1984, 1702; Page; van Niel; Westwood *J. Chem. Soc., Perkin Trans. 1* 1988, 269.

⁶⁹⁴For reviews, see Friedrich, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 2; Wiley: New York, 1983, pp. 1345-1390; Friedrich; Wallenfels, in Rappoport, Ref. 334, pp. 72-77.

⁶⁹⁵For reviews of Me_3SiCN and related compounds, see Rasmussen; Heilmann; Krepski *Adv. Silicon Chem.* 1991, 1, 65-187; Groutas; Felker *Synthesis* 1980, 861-868. For procedures using Me_3SiCl and CN^- instead of Me_3SiCN , see Yoneda; Santo; Harusawa; Kurihara *Synthesis* 1986, 1054; Sukata *Bull. Chem. Soc. Jpn.* 1987, 60, 3820.

^{695a}Kobayashi; Tsuchiya; Mukaiyama *Chem. Lett.* 1991, 537.



the reaction between Me_3SiCN and aromatic aldehydes or ketones gives α -chloro nitriles $\text{Cl}-\text{CRR}'-\text{CN}$.⁶⁹⁶

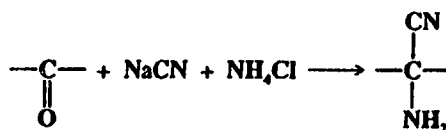
Frequently it is the bisulfite addition product that is treated with CN^- . This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin in situ to the corresponding α -hydroxy acid. This reaction is important in the *Kiliani-Fischer* method of extending the carbon chain of a sugar.

The addition is nucleophilic and the actual nucleophile is CN^- , so the reaction rate is increased by the addition of base.⁶⁹⁷ This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.⁶⁹⁸

The reaction has been carried out enantioselectively: optically active cyanohydrins were prepared with the aid of optically active catalysts.⁶⁹⁹

OS I, 336; II, 7, 29, 387; III, 436; IV, 58, 506; VI, 307; VII, 20, 381, 517, 521. For the reverse reaction, see OS III, 101.

6-50 The Strecker Synthesis Cyano,amino-de-oxo-bisubstitution



α -Amino nitriles⁷⁰⁰ can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl . This is called the *Strecker synthesis*;^{700a} it is a special case of the Mannich reaction (6-16). Since the CN is easily hydrolyzed to the acid, this is a convenient method for the preparation of α -amino acids. The reaction has also been carried out with $\text{NH}_3 + \text{HCN}$ and with NH_4CN . Salts of primary and secondary amines can be used instead of NH_4^+ to obtain N -substituted and N,N -disubstituted α -amino nitriles. Unlike 6-49, the Strecker synthesis is useful for aromatic as well as aliphatic ketones. As in 6-49, the Me_3SiCN method has been used; 64 is converted to the product with ammonia or an amine.⁷⁰¹

OS I, 21, 355; III, 66, 84, 88, 275; IV, 274; V, 437; VI, 334.

⁶⁹⁶Kiyooka; Fujiyama; Kawaguchi. *Chem. Lett.* 1984, 1979.

⁶⁹⁷For a review, see Ogata; Kawasaki, in Zabicky *The Chemistry of the Carbonyl Group*, vol. 2, Wiley: New York, 1970, pp. 21-32. See also Okano; do Amaral; Cordes *J. Am. Chem. Soc.* 1976, 98, 4201; Ching; Kallen *J. Am. Chem. Soc.* 1978, 100, 6119.

⁶⁹⁸Lapworth *J. Chem. Soc.* 1903, 83, 998.

⁶⁹⁹See Minamikawa; Hayakawa; Yamada; Iwasawa; Narasaka *Bull. Chem. Soc. Jpn.* 1988, 61, 4379; Jackson; Jayatilake; Matthews; Wilshire *Aust. J. Chem.* 1988, 41, 203; Garner; Fernández; Gladysz *Tetrahedron Lett.* 1989, 30, 3931; Mori; Ikeda; Kinoshita; Inoue *Chem. Lett.* 1989, 2119; Kobayashi; Tsuchiya; Mukaiyama *Chem. Lett.* 1991, 541, and references cited in these papers.

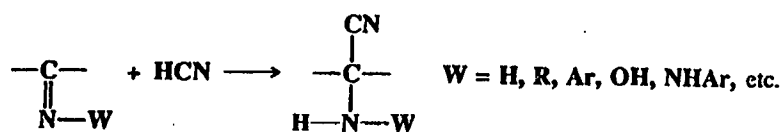
⁷⁰⁰For a review of α -amino nitriles, see Shafran; Bakulev; Mokrushin *Russ. Chem. Rev.* 1989, 58, 148-162.

^{700a}For a review of asymmetric Strecker syntheses, see Williams *Synthesis of Optically Active α -Amino Acids*; Pergamon: Elmsford, NY, 1989, pp. 208-229.

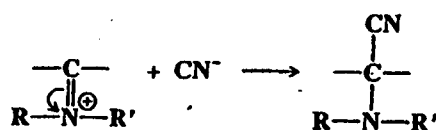
⁷⁰¹See Mai; Patil *Tetrahedron Lett.* 1984, 25, 4583; *Synth. Commun.* 1985, 15, 157.

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6-51 The Addition of HCN to C=N and C≡N Bonds
N-Hydro-C-cyano-addition

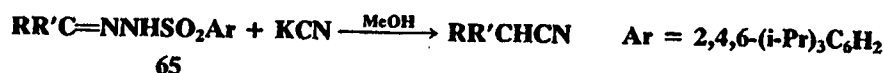


HCN adds to imines, Schiff bases, hydrazones, oximes, and similar compounds. CN⁻ can be added to iminium ions.⁷⁰⁰

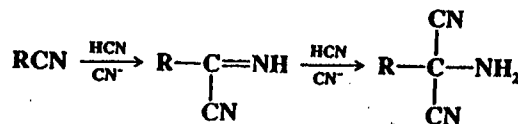


As in 6-48, the addition to imines has been carried out enantioselectively.⁷⁰²

The addition of KCN to triisopropylbenzenesulfonyl hydrazones 65 provides an indirect method for achieving the conversion RR'CO → RR'CHCN.⁷⁰³ The reaction is successful for hydrazones of aliphatic aldehydes and ketones.

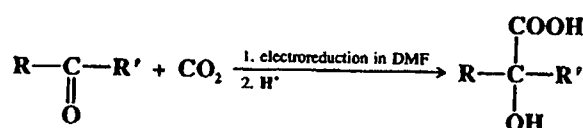


HCN can also be added to the C≡N bond to give iminonitriles or α-aminonitriles.⁷⁰⁴



OS V, 344. See also OS V, 269.

6-52 The Addition of CO₂ to Aldehydes and Ketones
O-Hydro-C-carboxyl-addition



⁷⁰²Saito; Harada *Tetrahedron Lett.* 1989, 30, 4535.

⁷⁰³Jiricny; Orere; Reese *J. Chem. Soc., Perkin Trans. 1* 1980, 1487. For other methods of achieving this conversion, see Ziegler; Wender *J. Org. Chem.* 1977, 42, 2001; Cacchi; Caglioti; Paolucci *Synthesis* 1975, 120; Yoneda; Harusawa; Kurihara *Tetrahedron Lett.* 1989, 30, 3681; Okimoto; Chiba *J. Org. Chem.* 1990, 55, 1070.

⁷⁰⁴For an example, see Ferris; Sanchez *Org. Synth.* V, 344.