New Applications of 2,4,6-Trichloro-1,3,5-triazine (TT) in Synthesis: Highly Efficient and Chemoselective Deprotection and Ring-Enlargement of Dithioacetals and Oxathioacetals

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Abstract: Efficient deprotection of a wide variety of 1,3-dithioacetals and 1,3-oxathiolanes to the corresponding carbonyl compounds at room temperature using a combination of 2,4,6-trichloro-1,3,5-triazine (TT) and dimethyl sulfoxide (DMSO) was investigated. In this way, 1,3-oxathioacetals and 1,3-dithioacetals of enolizable ketones were converted to the corresponding 1,4-oxathiepine and 1,4-dithiepine derivatives, respectively.

Key words: chemoselective, 1,3-dithioacetals, 1,3-oxathiolanes, carbonyl compounds

Acetals, thioacetals, and oxathioacetals are the most commonly utilized protecting groups for carbonyl compounds in many syntheses of reasonable complexity.[1] Among the various functional groups, the protection of carbonyl groups especially as 1,3-oxathioacetals and dithioacetals, is an important one owing to their application as acyl anion equivalent displaying a reactivity umpolung in carbon-carbon bond forming reactions.[2] 1,3-Oxathioacetals are also valuable starting materials for the enantioselective synthesis of α-hydroxyaldehydes and related compounds, first introduced by Eliel and his co-workers[3] and later on studied by others.[4] In addition, 1,3-oxathioacetals are considerably more stable than the corresponding *O,O*-acetals under acidic conditions and also easier to remove than the corresponding *S,S*-acetals. Typically, deprotection of thioacetals requires drastic conditions or toxic reagents such as mercury salts,[5] other heavy metals,[6] ceric ammonium nitrate (CAN),[7] SeO_2.[8] In addition, some methods have been reported employing $Pb(OAc)_4$ and $Tl(O_2CCF_3)_3$.[9] A few non-metallic reagents such as the oxide of nitrogen,[10a] trisethyloxonium tetrafluoroborate,[10b] and methyl fluorosulfonate[10c] were also applied for this purpose. Recently, a number of reagents such as $Bi(NO_3)_3$,[11a] clay-$Fe(NO_3)_3$,[11b] bis(trifluroacetoxy)iodobenzene,[11c] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[11d] SiO_2-Cl/DMSO,[11e] $[Zr(OPMe_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}]$,[11f] and natural kaolenite[11g] have also been developed for the selective deprotection of dithioacetals. Though a large number of methods are developed for cleavage of dithioacetals, only a few methods are available in the literature for oxathioacetals. Among the earlier work, there are a few processes known for the deprotection of oxathioacetals employing isoamyl nitrite,[12a] and chloramines-T.[12b] Recently, TMSOTf alone,[13] or in the presence of both 4-nitrobenzaldehyde,[14] and polymer supported 4-nitrobenzaldehyde,[15] have also been reported as the reagent of choice for this transformation. However, these methods suffered from drawbacks such as the difficulty of removal of the by-product oxathioacetal derived from p-nitrobenzaldehyde[14] or the use of expensive polymer supported reagent,[15] and sometimes they fail to deprotect non-benzylic oxathioacetals.[13] Some other well-known protocols are based on halonium ion sources such as NCS–$AgNO_3$,[3a] I_2–$AgNO_2$,[16] NBS in aqueous acetone,[17] and organic ammonium tribromide[18] for deprotection of a wide variety of oxathioacetals. Unfortunately, these methods also involve the use of a molar excess of expensive silver salts,[3a,16] require long reaction times,[17,18] or involves expensive organic tribromides.[18] Very recently, another method was also reported by using a catalytic amount of trichlorooxyvanadium which also requires drastic conditions.[19] Therefore, it seems that the development of new mild protocols for deprotection of both dithioacetals and oxathioacetals is being still pursued.

The pioneering work of Senier showed that 2,4,6-trichloro-1,3,5-triazine (TT) could function as a highly oxophilic reagent for the conversion of carboxylic acids to the corresponding acid chlorides.[20] The use of TT as a chemical reagent has been previously reported for converting carboxylic acids into chlorides, esters, amides, peptides, and macrolactones,[21,22] for mild and selective reduction of carboxylic acids,[23] synthesis of α-diazoketones,[24] deoxygenation of sulfoxides,[25] synthesis of β-lactams,[26] formylation of alcohols,[27] modified Swern oxidation of alcohols,[28] conversion of alcohols to halides,[29] and oxidative coupling of thiols to disulfides.[30] In our previous work regarding the use of WCl_6[31] and SiO_2Cl (silica chloride)[11e] as powerful oxophilic reagents, we demonstrated that a combination of these reagents with DMSO could be utilized for various types of oxidative transformation such as either ring enlargement of 1,3-dithiolanes and 1,3-dithianes or deprotection of thioacetals via an in situ formation of electrophilic chlorine species (e.g. chloro dimethylsulfonium ions). Unfortunately, these procedures have drawbacks such as the use of expensive and highly unstable WCl_6 or involves laborious and time consuming steps for preparation of SiO_2Cl. However, TT is a rather

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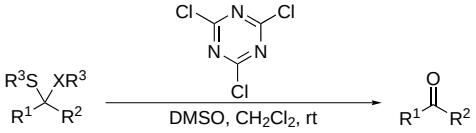
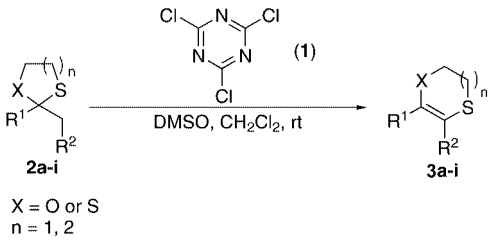
cheap reagent and its use does not need special precautions. Moreover, the absence of problems of disposing of the waste product and the high degree of selectivity through the reaction of TT with organic molecules are key promising features for its future application in both industrial and synthetic transformations.[32] Owing to the relatively strong oxophilic nature of TT, we hypothesized that this reagent might be show a similar behavior as WCl_6, and SiO_2Cl in promoting similar transformations. Along this line, herein, we wish to report a very mild and chemoselective protocol for the efficient conversion of 1,3-dithioacetals and 1,3-oxathioacetals to the corresponding carbonyl compounds (Scheme 1).



Scheme 1

Inspection of the data in Table 1 shows that using this protocol, various types of both open-chain and cyclic dithioacetals as well as 1,3-oxathioacetals of aromatic aldehydes can effectively be converted to the corresponding carbonyl compounds in good to excellent yields (entries 1–18). The reactions are generally clean and fast and are completed within 1–3 h. In a similar way, dithioacetals and oxathioacetals of aliphatic- as well as cinnamaldehyde also furnished the parent aldehydes in good to excellent yields (Table 1, entries 19–25). It is worth mentioning that 1,3-dithioacetals and 1,3-oxathioacals derived from the corresponding ketones show quiet different behavior depending on the nature of both R^1 and R^2 groups. If both R^1 and R^2 groups were non-enolizable groups, employing the above-mentioned procedure would lead to the corresponding ketones almost in quantitative yields (Table 1, entries 26 and 27). On the other hand, in the case that either R^1 or R^2 are enolizable the corresponding rearranged products such as dithiepines, dithiins, or oxathiepines were formed as the sole products (Scheme 2, Table 2).



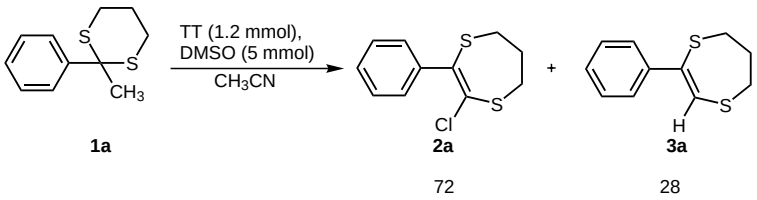
Scheme 2

When a mixture of 2-methyl-2-phenyl-1,3-dithiolane was treated with TT (0.5 equiv) and DMSO (4 equiv) in anhyd CH_2Cl_2, the corresponding 2-chloro-6,7-dihydro-3-phenyl-5*H*-[1,4]dithiepine was formed in good yield as sole product (Table 2, entry 1). Surveying the literature reveals that though the ring-enlargement of 1,3-dithianes, 1,3-dithiolanes, and 1,3-oxathiolanes can be successfully applied as a tool for both the construction of larger sulfur-containing heterocyclic rings and also 1,2-transposition of carbonyl compounds, there are few examples of this transformation in the literature.[11e,31,33] Furthermore, almost all of the present protocols involve expensive,[31,33f,g] highly acidic[11e,33d] or very toxic reagents [33f,g] and the yields of the products are not always satisfactory. Therefore, the present TT-based protocol is the first example of such a transformation that approaches the problem from points of view of mildness of the reaction conditions, inexpensiveness of the reagents, and also the absence of toxic waste disposal.

It is also important to note that the nature of the solvent plays an important role on the product distribution since, for example in nucleophilic solvents such as CH_3CN a mixture of both chlorinated (**2a**) and non-chlorinated (**3a**) dithiepine was produced (Scheme 3).

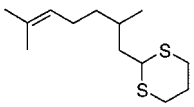
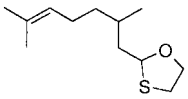
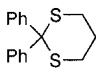
In summary, we have introduced a new application for 2,4,6-trichloro-1,3,5-triazine. High yields of the products, the absence of the toxic waste disposal, short reaction times, and also mild reaction conditions make this protocol as an alternative to the existing methods. Further applications of TT in organic transformation are currently in progress in our laboratories.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 250 or 500 MHz spectrometer in $CDCl_3$ and with TMS as internal standard. All of the products are known and gave satisfactory IR and NMR spectra.



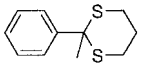
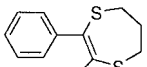
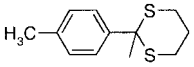
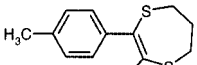
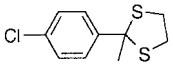
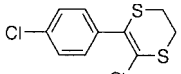
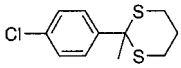
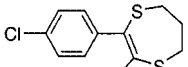
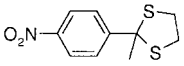
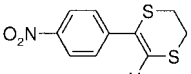
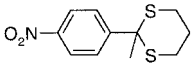
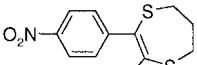
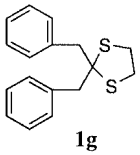
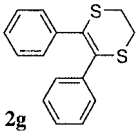
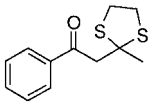
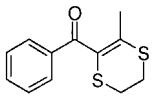
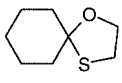
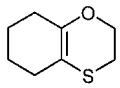
Scheme 3 Product distribution was determined by using a careful analysis of the ^{1}H NMR (500 MHz) spectra of the crude products for integration of vinylic protons with those of aromatic ring.

Table 1 Deprotection of Thioacetals and Oxathioacetals with TT/DMSO in CH_2Cl_2

Entry	R^1	R^2	R^3	X	Time (h)	Yield (%)[a, b]
1	H	C_6H_5	$-CH_2CH_2-$	S	3	90
2	H	4-F-C_6H_4	$-CH_2CH_2-$	S	3.5	93
3	H	4-CH_3O-C_6H_4	$-CH_2CH_2-$	S	2.5	92
4	H	4-*i*-Pr-C_6H_4	$-CH_2CH_2-$	S	2.45	93
5	H	C_6H_5	$-CH_2CH_2-$	O	1	91
6	H	4-NO_2-C_6H_4	$-CH_2CH_2-$	O	3	90
7	H	3,5-diCH_3O-C_6H_3	$-CH_2CH_2-$	O	1.5	90
8	H	C_6H_5	$-CH_2CH_2CH_2-$	S	1.5	92
9	H	4-CH_3O-C_6H_4	$-CH_2CH_2CH_2-$	S	1.5	95
10	H	4-CH_3S-C_6H_4	$-CH_2CH_2CH_2-$	S	1	93
11	H	4-*i*-Pr-C_6H_4	$-CH_2CH_2CH_2-$	S	1	94
12	H	4-Cl-C_6H_4	$-CH_2CH_2CH_2-$	S	2.5	92
13	H	2,5-$(CH_3O)_2$-C_6H_3	$-CH_2CH_2CH_2-$	S	1	90
14	H	2,6-$(Cl)_2$-C_6H_3	$-CH_2CH_2CH_2-$	S	2.15	91
15	H	3-Br-C_6H_4	$-CH_2CH_2CH_2-$	S	2	92
16	H	3-PhO-C_6H_4	$-CH_2CH_2CH_2-$	S	2	94
17	H	2-Naphthyl	$-CH_2CH_2CH_2-$	S	1	94
18	H	Cinnamyl	$-CH_2CH_2CH_2-$	S	1	89
19	H	*n*-C_6H_{13}	$-CH_2CH_2CH_2-$	S	1.5	90
20					2	85
21					1	89
22	H	$-C_6H_4$	$-C_6H_5$		1	90
23	H	$-C_6H_4$	$-CH_2-C_6H_5$		1	92
24	H	Cinnamyl	$-C_6H_5$		1.2	88
25	H	Cinnamyl	$-CH_2-C_6H_5$		1	85
26					2.5	96
27					2	95

[a] The ratio substrate/TT/DMSO is: 1.0:0.5:5.0.
[b] Yields refer to isolated products.

Table 2 Ring-Expansion Chlorination of 1,3-Dithiolanes and 1,3-Dithianes and 1,3-Oxathiolane by TT/DMSO in CH_2Cl_2

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b,c]
1	 **1a**	 **2a**	1.5	80
2	 **1b**	 **2b**	1.1	85
3	 **1c**	 **2c**	2	81
4	 **1d**	 **2d**	2.1	82
5	 **1e**	 **2e**	1.5	86
6	 **1f**	 **2f**	1.6	88
7	 **1g**	 **2g**	1.5	81
8	 **1h**	 **2h**	1.6	87
9	 **1i**	 **2i**	1.5	86

[a] The ratio substrate/TT/DMSO is: 1.0:1.2:5.0.
[b] Isolated yields.
[c] All of the products are known and gave satisfactory ^1H and ^{13}C NMR spectra in comparison with those of authentic samples (see ref.[11e,31]).

Deprotection of Thioacetals and Oxathioacetals with DMSO/TT; General Procedure

To a solution of thioacetal (2 mmol) and anhyd DMSO (0.78–0.94 g, 10–12 mmol) in anhyd CH_2Cl_2 (10 mL), TT (0.184 g, 1 mmol) was added. The mixture was stirred at r.t. for the appropriate reaction time (Table 1). After completion of the reaction (TLC), the reaction was quenched with an aq solution of NaOH (5% w/v, 10 mL). The organic layer was separated, and the aq layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were then washed with water (2 × 15 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded the almost pure product. Further purification was achieved by column chromatography using EtOAc–*n*-hexane (1:10) as eluent.

Ring Expansion of 2,2-Bis(benzyl)-1,3-dithiolane to the Corresponding Dihydro-1,4-dithiin with DMSO/TT in Anhyd CH_2Cl_2; Typical Procedure

To a solution of 2,2-bis(benzyl)-1,3-dithiolane (1g, 1.0 mmol) and anhyd DMSO (0.39 g, 5.0 mmol) in anhyd CH_2Cl_2, TT (0.22 g, 1.2 mmol) was added. The reaction mixture was stirred at r.t. for 1.5 h. Then, the reaction mixture was quenched with an aq solution of NaOH (5% w/v, 10 mL) and extracted with CH_2Cl_2. The organic extracts were combined and washed with water (2 × 15 mL), separated and dried over Na_2SO_4. Evaporation of the solvent gave the crude product. Purification by means of column chromatography with silica gel using CCl_4 as eluent affords the pure product as purple-red viscous liquid (0.23 g, 81% yield).[11e]

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References

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**. (b) Kocienski, P. J. *Protecting Groups*; Thieme: New York, **1994**.
(2) (a) Fuji, K.; Ueda, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1977**, 814. (b) Fuji, K.; Ueda, M.; Sumi, K.; Kajiwara, K.; Fujita, E.; Iwashita, T.; Miura, I. *J. Org. Chem.* **1985**, *50*, 657. (c) Fuji, K.; Ueda, M.; Sumi, K.; Fujita, E. *Tetrahedron Lett.* **1981**, *22*, 2005. (d) Fuji, K.; Ueda, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1983**, 49.
(3) (a) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943. (b) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937. (c) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1985**, *26*, 3907. (d) Eliel, E. L.; Soai, K. *Tetrahedron Lett.* **1981**, *21*, 2859.
(4) (a) Isobe, M.; Obeyama, J.; Funabashi, Y.; Goto, T. *Tetrahedron Lett.* **1988**, *29*, 4773. (b) Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc.* **1990**, *112*, 8189.
(5) (a) Degani, I.; Fochi, R.; Regondi, V. *Synthesis* **1981**, 51. (b) Fujita, E.; Nagao, Y.; Kanero, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743.
(6) (a) Ghringhelli, D. *Synthesis* **1982**, 580. (b) Liu, H. J.; Winszniewski, V. *Tetrahedron Lett.* **1988**, *29*, 5471.
(7) Ho, T. L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.
(8) Haroutounian, S. A. *Synthesis* **1995**, 39.
(9) (a) Rotermund, G. W. *Houben-Weyl, Methoden der Organischen Chemie*, Vol. 4/1b; Müller, E., Ed.; Thieme: Stuttgart, **1975**, 407. (b) Ho, T. L.; Wong, C. M. *Can. J. Chem.* **1972**, *50*, 3740.
(10) (a) Mehta, G.; Uma, R. *Tetrahedron Lett.* **1996**, *37*, 1879. (b) Oishi, T.; Kamemoto, K.; Ban, Y. *Tetrahedron Lett.* **1972**, *11*, 1085. (c) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1977**, 680.
(11) (a) Komatsu, N.; Tanguchi, A.; Uda, M.; Suzuki, H. *Chem. Commun.* **1996**, 1847. (b) Balogh, M.; Cornelis, A.; Laszlo, P. *Tetrahedron Lett.* **1984**, *25*, 3313. (c) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287. (d) Tanemura, K.; Dohya, H.; Imamura, M.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 453. (e) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H.; Karimi, B. *J. Org. Chem.* **2002**, *67*, 2572; and references cited therein. (f) Curini, M.; Marcotullio, M. C.; Pisani, E.; Rosati, O. *Synlett* **1997**, 769. (g) Bandgar, B. P.; Kasture, S. P. *Green Chem.* **2000**, *2*, 154.
(12) (a) Fuji, K.; Ichikawa, K.; Fujita, E. *Tetrahedron Lett.* **1978**, 3561. (b) Emerson, D. W.; Wynberg, H. *Tetrahedron Lett.* **1971**, 3445.
(13) Ravindranathan, T.; Chavan, S. P.; Dantale, S. W. *Tetrahedron Lett.* **1995**, *36*, 2285.
(14) (a) Ravindranathan, T.; Chavan, S. P.; Tejwani, R. B.; Varghese, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1750. (b) Ravindranathan, T.; Chavan, S. P.; Varghese, J. P.; Dantale, S. W.; Tejwani, R. B. *J. Chem. Soc., Chem. Commun.* **1994**, 1937.
(15) Ravindranathan, T.; Chavan, S. P.; Awachat, M. M. *Tetrahedron Lett.* **1994**, *35*, 8835.
(16) (a) Nishide, K.; Yokota, K.; Nakamura, D.; Sumiya, T.; Node, M.; Ueda, M.; Fuji, K. *Tetrahedron Lett.* **1993**, *34*, 3425. (b) Nishide, K.; Yokota, K.; Nakamura, D.; Sumiya, T.; Node, M.; Ueda, M.; Fuji, K. *Heterocycles* **1997**, *44*, 393.
(17) Karimi, B.; Seradj, H.; Tabaei, M. H. *Synlett* **2000**, 1798.
(18) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *Tetrahedron Lett.* **2002**, *43*, 2843.
(19) Kirihara, M.; Ochiai, Y.; Aria, N.; Takizawa, S.; Momose, T.; Nemoto, H. *Tetrahedron Lett.* **1999**, *40*, 9055.
(20) Senier, A. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 311.
(21) Venkataraman, K.; Wagle, D. R. *Tetrahedrom Lett.* **1979**, 3037.
(22) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1980**, *21*, 1893.
(23) Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* **1999**, *40*, 4395.
(24) Forbes, D. C.; Barrett, E. J.; Lewis, D. L.; Smith, M. C. *Tetrahedron Lett.* **2000**, *41*, 9943.
(25) Manhas, M. S.; Bose, A. K.; Khajavi, M. S. *Synthesis* **1981**, 209.
(26) Olah, G. A.; Fung, A. P.; Gupta, B. G. B.; Narang, S. C. *Synthesis* **1980**, 221.
(27) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 5152.
(28) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907.
(29) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553; and references cited therein.
(30) Karimi, B.; Hazarkhani, H.; Zareyee, D. *Synthesis* **2002**, 2513.
(31) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett* **1999**, 413.
(32) Crenova Inc.; XX, Z. *Org. Proc. Res. Dev.* **2002**, *6*, 354.
(33) (a) Chen, C. H. *Tetrahedron Lett.* **1976**, 25. (b) Chen, C. H.; Donatelli, B. A. *J. Org. Chem.* **1976**, *41*, 3053. (c) Janssen, J. W. A. M.; Kwart, H. *J. Org. Chem.* **1977**, *42*, 1530. (d) Bulman-Page, P. C.; Ley, S. V.; Morton, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 457. (e) Francisco, C. G.; Freire, R.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1621. (f) Tani, H.; Inamasu, T.; Tamura, R.; Suzuki, H. *Chem. Lett.* **1990**, 1323. (g) Tani, H.; Inamasu, T.; Masumoto, K.; Tamura, R.; Shimizu, H.; Suzuki, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *67*, 261.