Iodine-Catalyzed, Efficient and Mild Procedure for Highly Chemoselective Acetalization of Carbonyl Compounds under Neutral Aprotic Conditions

Babak Karimi,* Behzad Golshani

Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), P.O.Box 45195-159, Gava Zang, Zanjan, Iran
Fax +98(241)4249023; E-mail: Karimi@iasbs.ac.ir

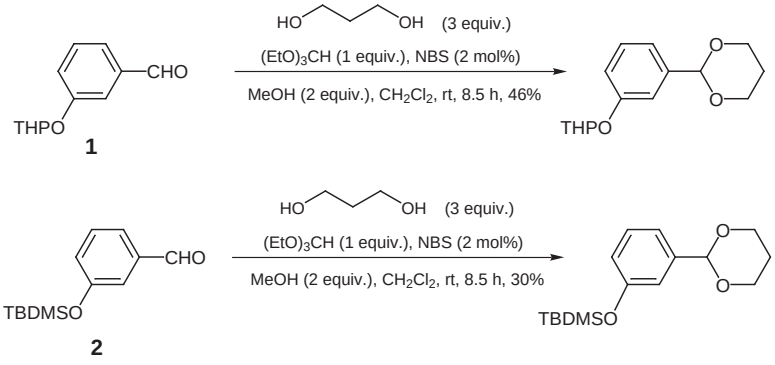
Received 2 January 2002; revised 14 March 2002

Abstract: Various types of carbonyl compounds are efficiently converted to their 1,3-dioxanes by the use of 1,3-bis(trimethylsiloxy)propane (BTSP) and a catalytic amount of iodine (3–7 mol%) under essentially neutral aprotic condition.

Key words: carbonyl compounds, chemoselectivity, protection, 1,3-bis(trimethylsiloxy)propane, iodine

The protection of carbonyl compounds or diols as acetals is of paramount importance in organic synthesis, as shown by a large number of methods that have been developed for this key transformation.[1,2] Moreover, chiral acetals are particularly important precursor for the preparation of enantiomerically pure compounds.[3] An interesting challenging problem during many syntheses of reasonable complexity is how to protect a carbonyl group in the presence of a wide variety of sensitive functional groups. Unfortunately, despite the importance of this transformation less attention has been paid to the development of mild protocols for acetalization of carbonyl compounds containing highly acid sensitive functional groups. Among the plethora of procedures typically established for preparation of acetals,[1] a few work under considerable mild reaction conditions.[4] It has been shown earlier by Noyori et al.[4a] that dioxolanation of carbonyl compounds under aprotic conditions are readily achieved by 1,2-bis(trimethylsiloxy)ethane in the presence of catalytic amounts of super acid trimethylsilyl trifluoromethanesulfonate (TMSOTf). Recently, a systematic study on this protocol by Hwu et al.[4c] has revealed that the acid-sensitive groups such as THP-ethers were relatively resistant toward the reaction condition only at –78 °C accompanied by the considerable formation of 1,2-bis(tetrahydropyranloxy)ethane.[4c] However this protocol suffered from a drawback which may puts some restriction on its scope. Deprotection of THP-ethers occurred when the reaction mixture was warmed to room temperature. Moreover, TMSOTf is rather expensive and also highly moisture sensitive reagent. Therefore, there is still much room for improvement, however, for this acetalization reaction. In our development of new methods for functional group transformation, we are especially interested in exploring the potential uses of various types of neutral catalysts.[5] During these studies we have found that NBS is a chemoselective catalyst for 1,3-dioxanation of various types of carbonyl compounds in the presence of some acid-sensitive substrates such as aliphatic THP- and TBDMS-ethers.[4d] However, in continuation of this study we discovered that the NBS protocol was unable to selectively convert more labile acid-sensitive phenolic ethers such as **1**, **2** to the corresponding 1,3-dioxanes, because the highly acid sensitive phenolic ethers interfere with the selective protection of carbonyl function (Scheme 1).

This observation encouraged us to find a milder catalytic method that would allow survival of more acid-labile phenolic THP- and TBDMS ethers. Very recently, we discovered that iodine effectively catalyzes trimethylsilylation of highly acid labile diarylalkyl carbinol using hexame-



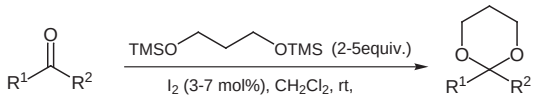
Scheme 1

Synthesis 2002, No. 6, 29 04 2002. Article Identifier:
1437-210X,E;2002,0,06,0784,0788,ftx,en;Z00502SS.pdf.

ISSN 0039-7881

thyldisilazane (HMDS).[6] With this observation in mind, we hypothesized that iodine might be a suitable and mild substitute for TMSOTf in Noyori's protocol. Iodine is a cheap and easy available reagent and its application does not need special precautions. Along this line, herein, we wish to describe our last finding on neutral and aprotic acetalization of carbonyl compounds using iodine as catalyst. In this regard, we have observed that 1,3-dioxanes of simple aldehydes as well as α,β-unsaturated aldehydes could be prepared using 1,3-bistrimethylsiloxy propane (BTSP) in the presence of catalytic amounts of I_2 (3 mol%) under neutral and aprotic conditions (Table 1, entries 1–11). Different types of aliphatic and aromatic ketones were also converted to their acetals in satisfactory yields although after relatively prolonged reaction time (Table 1, entries 12–18). Interestingly, under the described reaction conditions even highly hindered ketones smoothly furnished the corresponding acetals in good yields (Table 1, entries 19,20). It is worth mentioning, because similar transformation using NBS protocol afforded poor yields of the corresponding acetals.[3] 2-Furaldehyde as a model for highly sensitive *pseudo* enal substrate was also converted to corresponding 1,3-dioxane in excellent yield (Table 1, entry 21). Furthermore, the presented method even tolerates a range of functional groups such as phenolic esters, and highly acid sensitive THP and TBDMS ethers (Table 1, entries 22–27). It is worth mentioning that in the case of substrates comprising double bonds, no double bond migration was observed after careful inspection of 500 MHz NMR spectra (Table 1, entry 11,27). Based on reactivity difference between aldehydes and ketones, we have also monitored chemoselective acetalization of aldehydes in the presence of ketones. Interestingly, benzaldehyde, 4-chlorobenzaldehyde, and valeraldehyde were converted to their acetals in the presence of acetophenone, 4-chloroacetophenone and benzylacetone, respectively, with high degree of chemoselectivity (Scheme 2).

Table Acetalization of Carbonyl Compounds under Neutral Aprotic Conditions using BTSP in the Presence of Iodine



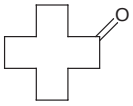
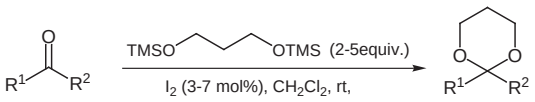
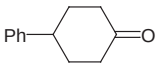
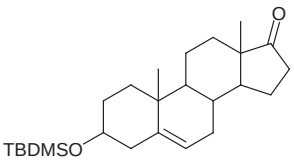
Entry	R^1	R^2	Subst./BTSP/I_2	Time (h)	Yield (%)[a]
1	Ph	H	1:2:0.03	17	90
2	Ph	H	1:1.5:0.03	11	95[b]
3	4-ClC_6H_4	H	1:2:0.03	20	97
4	4-BrC_6H_4	H	1:2:0.03	23	89
5	4-MeC_6H_4	H	1: 2:0.03	18	93
6	4-$MeOC_6H_4$	H	1: 2:0.03	15.5	93
7	3-$NO_2C_6H_4$	H	1: 2:0.03	27.5	91
8	3-MeC_6H_4	H	1: 2:0.03	18	85
9	PhCH=CH	H	1:2:0.03	19	95
10	Bu	H	1: 2:0.03	18	91
11	Citral (*cis* + *trans*)		1:2:0.03	22	89[b]
12	Ph	CH_3	1:2:0.04	66	94
13	4-$NO_2C_6H_4$	CH_3	1:2:0.04	72	95
14	4-PhC_6H_4	CH_3	1:2:0.04	71	75
15	4-$MeOC_6H_4$	CH_3	1:2:0.04	96	92
16	$PhCH_2CH_2$	CH_3	1:3:0.03	72	80
17			1:2:0.03	65	92

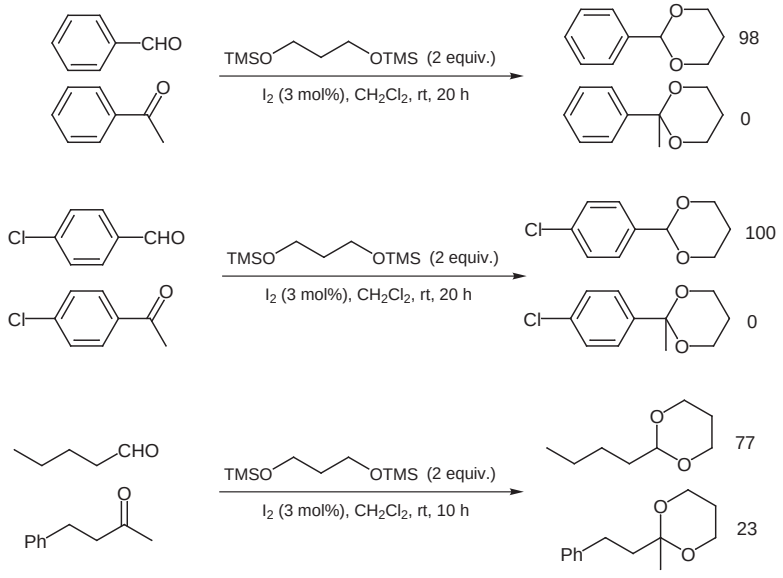
Table Acetalization of Carbonyl Compounds under Neutral Aprotic Conditions using BTSP in the Presence of Iodine (continued)



Entry	R^1	R^2	Subst./BTSP/I_2	Time (h)	Yield (%)[a]
18			1:2:0.03	49	91
19	Ph	Ph	1:5:0.07	168	83
20	(–)-camphor		1:5:0.07	168	70[c]
21	Furyl	H	1:2:0.03	20	80
22	4-($PhCO_2$)C_6H_4	H	1:2:0.03	18.5	96
23	2-($PhCO_2$)C_6H_4	H	1:2:0.03	25	97
24	4-(THPO)C_6H_4	H	1:3.5:0.03	59	75[c]
25	3-(THPO)C_6H_4	H	1:2:0.03	16	91
26	3-(TBDMSO)C_6H_4	H	1:2:0.03	16	87
27			1:5:0.07	196	20[c, d]

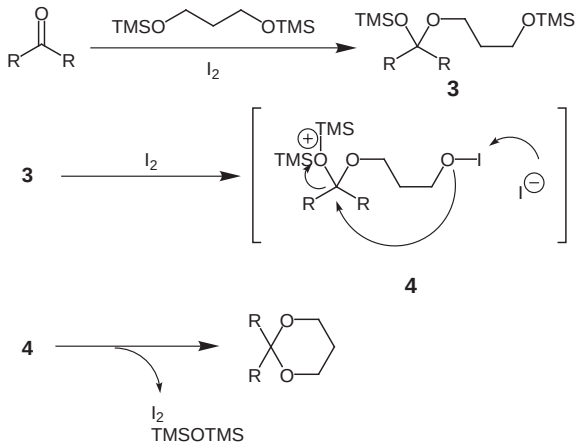
[a] Yields refer to isolated pure product unless otherwise stated.
[b] Bis(trimethylsiloxy)ethane (BTSE) was used.
[c] Yields based on NMR of the crude products.
[d] No deprotection of silyl group was observed and the residue of starting substrate was recovered intact.

The actual mechanism for this iodine-catalyzed acetalization is unclear. However, as we have mentioned in our previous paper, iodine might act as a Lewis acid. Therefore, a plausible mechanism is that I_2 catalyzes a set of *silyl exchange* reactions between BTSP and carbonyl oxygen to produce the key intermediate **4**. Irreversible cy-



Scheme 2

clization of this intermediate then lead to cyclic acetal, hexamethyldisiloxane (HMDS) and concomitant release of I_2 that reenter the catalytic cycle (Scheme 3). The formation of stable HMDS could be considered as the driving force for the reactions. Nevertheless, the actual mechanism of this transformation should be studied in detail.



Scheme 3

In conclusion, we have developed a remarkably mild and catalytic protocol for the acetalization of a relatively wide range of carbonyl compounds. To the best of our knowledge this is the first example of such a transformation under neutral aprotic conditions. Further investigations on the development of organic transformations under neutral aprotic conditions using iodine and other neutral catalyst are ongoing in our laboratories.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 250 or 500 MHz spectrometer in $CDCl_3$ as the solvent and TMS as internal standard at 25 °C. The majority of the products are known and all of the isolated products gave satisfactory IR spectra.

Iodine-Catalyzed Acetalization of Carbonyl Compounds; General Procedure

To a solution of carbonyl compound (2 mmol), BTSP (4–6 mmol) in anhyd CH_2Cl_2 (20 mL) was added I_2 (0.06–0.14 mmol), and the resulting solution was stirred at r.t. After completion of the reaction (TLC or GC), a cold 10% aq solution of NaOH (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were washed successively with $Na_2S_2O_3$ solution (5%, 15 mL), H_2O (2 × 15 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave almost pure product(s). Further purification was proceeded by vacuum distillation or recrystallization in appropriate solvent to afford pure acetals (Table).

Some representative spectral data are as follows:

2-(4-Chlorophenyl)-1,3-dioxane (Entry 3)

^{1}H NMR (250 MHz, $CDCl_3$, TMS):δ = 7.40–7.49 (d, *J* = 8.0 Hz, 2 H), 7.30–7.34 (d, *J* = 8.0 Hz, 2 H), 5.44 (s, 1 H), 4.20–4.26 (dd, *J* = 5.0, 11.3 Hz, 2 H), 3.88–3.98 (*pseudo*-t, *J* = 11.3 Hz, 2 H), 2.14–2.23 (tq, *J* = 5, 13.2 Hz, 1 H), 1.37–1.43 (quintet, *J* = 1.2, 13.2 Hz 1 H).

^{13}C NMR (63 MHz, $CDCl_3$, TMS): δ = 137.70, 134.95, 128.81, 127.91, 101.19, 67.78, 26.09.

2-(3-Nitrophenyl)-1,3-dioxane (Entry 7)

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 7.98–8.28 (d, *J* = 9.0 Hz, 2 H), 7.62–7.73 (d, *J* = 9.0 Hz, 2 H), 5.54 (s, 1 H), 4.24–4.51 (dd, *J* = 5, 13.8 Hz, 2 H), 3.94–4.05 (*pseudo*-t, *J* = 13.8 Hz, 2 H), 2.13–2.25 (tq, *J* = 5 Hz, *J* = 13.3 Hz, 1 H), 1.43–1.50 (quintet, *J* = 1.1, 13.3 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$, TMS): δ = 154.5, 147.05, 132.33, 127.50, 102.52, 67.80, 34.5.

2-Methyl-2-phenyl-1,3-dioxane (Entry 12)

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 7.16–7.37 (m, 5 H), 3.66–3.78 (m, 4 H), 1.94–2.08 (tq, *J* = 5.4, 12.9 Hz 1 H), 1.44 (s, 3 H), 1.11–1.19 (quintet, *J* = 1.2, 12.9 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$, TMS): δ = 141.63, 129.10, 128.99, 128.24, 100.92, 61.62, 32.84, 25.89.

2-Methyl-2-(2-phenylethyl)-1,3-dioxane (Entry 16)

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 6.91–7.38 (m, 5 H), 3.79–3.89 (m, 4 H), 2.73–2.79 (m, 2 H), 1.98–2.05 (m, 2 H), 1.97–1.73 (m, 1 H), 1.48–1.68 (m, 1 H), 1.44 (s, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$, TMS): δ = 139.01, 129.63, 129.65, 126.02, 100.85, 58.09, 41.50, 34.13, 23.67 18.27

1,5-Dioxaspiro[5.11]heptadecane (Entry 17)

^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ = 3.57–3.79 (m, 4 H), 1.59–1.66 (m, 6 H), 1.16–1.26 (br m, 18 H).

^{13}C NMR (63 MHz, $CDCl_3$, TMS): δ = 100.77, 60.28, 60.03, 40.30 (two peaks), 36.50, 30.29 (7 peaks), 19.25 (two peaks).

9-Phenyl-1,5-dioxaspiro[5.5]undecane (Entry 18)

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.29–7.32 (m, 2 H), 7.24–7.26 (m, 2 H), 7.18–7,22 (tt, *J* = 1.4, 7.2 Hz, 5 H), 3.97–4.00 (t, *J* = 5.7 Hz, 2 H), 3.93–3.95 (t, *J* = 5.7 Hz, 2 H), 2.56–2.60 (tt, *J* = 4.4, 11.7 Hz, 1 H), 2.40–2.45 (m, 2 H), 1.74–1.80 (m, 6 H), 1.47–1.54 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 154.93, 128.23, 126.57, 98.36, 55.01, 66.81, 33.73, 29.76, 28.36, 28.35.

2-(4-Benzoyloxyphenyl)-1,3-dioxane (Entry 22)

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 8.20-8.22 (dd, *J* = 8.4, 1.4 Hz, 2 H), 7.61–7.65 (tt, *J* = 7.4, 1.4 Hz, 1 H), 7.56–7.59 (d, *J* = 8.4 Hz, 2 H), 7.49–7.53 (t, *J* = 7.4 Hz, 2 H), 7.23–7.26 (dd, *J* = 8.4, 1.4 Hz, 2 H), 5.54 (s, 1 H), 4.27–4.30 (dd, *J* = 11.0, 3.6 Hz, 2 H), 3.98–4.03 (*pseudo*-t, *J* = 11.0 Hz, 2 H), 2.20–2.27 (tq, *J* = 5.0, 13.3 Hz, 1 H), 1.44–1.48 (quintet, *J* = 1.3, 13.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 165.08, 151.29, 136.58, 133.68, 130.25, 129.62, 128.65, 127.38, 121.55, 101.05, 67.45, 25.82.

2-[3-(Tetrahydropyran-2-yloxy)phenyl]-1,3-dioxane (Entry 24)

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.15–7.17 (t, *J* = 7.9 Hz, 1 H), 7.01–7.04 (d, *J* = 7.9 Hz, 1 H), 6.88–6.89 (t, *J* = 2.2 Hz, 1 H), 6.69–6.71 (dd, *J* = 7.9, 2.2 Hz, 1 H), 5.38 (s, 1 H), 4.52–4.53 (m, 1 H), 4.15–4.18 (dd, *J* = 11.0, 5.0 Hz, 2 H), 4.00–4.03 (m, 2 H), 3.86–3.91 (*pseudo*-t, *J* = 11.0 Hz, 2 H), 2.10–2.15 (tq, *J* = 5.0, 12.7 Hz, 1 H), 1.96–2.02 (m, 1 H), 1.81–1.85 (m, 1 H), 1.47–1.50 (m, 3 H), 1.34–1.37 (m, 1 H), 1.23–1.27 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 156.58, 140.11, 129.28, 119.13, 117.50, 115.83, 102.29, 98.79, 67.27, 66.81, 30.68, 30.67, 25.44, 19.51.

***tert*-Butyl-[3-(1,3-dioxane-2-yl)phenoxy]dimethylsilane (Entry 26)**

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ = 7.22–7.25 (t, *J* = 7.9 Hz, 1 H), 7.02–7.11 (d, *J* = 7.9 Hz, 1 H), 7.01 (t, *J* = 2.0 Hz, 1 H), 6.82–

6.84 (dd, *J* = 7.9, 2.0 Hz, 2 H), 5.46 (s, 1 H), 4.24–4.28 (dd, *J* = 11.0, 5.0 Hz, 2 H), 3.93–3.99 (*pseudo*-t, *J* = 11.0 Hz, 2 H), 2.17–2.26 (tq, *J* = 5, 12.4 Hz), 1.39–1.44 (quint, *J* = 2.4, 12.4 Hz, 1 H), 1.02 (s, 9 H), 0.23 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 155.62, 140.40, 129.21, 120.22, 119.02, 117.94, 101.38, 67.35, 25.82, 25.76, 18.20, –4.35.

Acknowledgement

The authors thank the *Institute for Advanced Studies in Basic Sciences* (IASBS) Research Council for support of this work.

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) For a review see: Meskens, A. J. *Synthesis* **1981**, 501. (b) For more recent leading references see: Shibagaki, M.; Takahashi, K.; Kuno, H.; Matsushita, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1258. (c) Ott, J.; Ramos Tombo, G. M.; Schmid, B.; Venanzi, L. M.; Wang, G.; Ward, T. R. *Tetrahedron Lett.* **1989**, *30*, 6151. (d) Otera, J.; Mizutani, T.; Nazaki, H. *Organometallics* **1989**, *8*, 2063. (e) Ma, S.; Venanzi, L. M. *Synlett* **1993**, 751. (f) Wang, W. B.; Shi, L. L.; Huang, Y. Z. *Tetrahedron Lett.* **1990**, *45*, 3315. (g) Corla, F.; Venanzi, L. M. *Helv. Chim. Acta* **1993**, *73*, 690. (h) Fukuzawa, S.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077; and references cited therein. (i) Tateiwa, J.; Horiuchi, H.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4039; and references cited therein.

(3) Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: Berlin, **1986**, 125–259.

(4) (a) Tsunodu, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (b) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3946. (c) Hwu, J. R.; Leu, L. C.; Robl, J. A.; Anderson, D. A.; Wetzel, J. M. *J. Org. Chem.* **1987**, *52*, 188. (d) Karimi, B.; Ebrahimian, G. R.; Seradj, H. *Org. Lett.* **1999**, *1*, 1737; and references cited therein.

(5) (a) Karimi, B.; Miri-Ashtiani, A. *Chem. Lett.* **1999**, 1199. (b) Karimi, B.; Seradj, H. *Synlett* **2000**, 641. (c) Karimi, B.; Seradj, H.; Ebrahimian, G. R. *Synlett* **1999**, 1456. (d) Karimi, B.; Seradj, H.; Tabaei, M. H. *Synlett* **2000**, 1798. (e) Firouzabadi, H.; Karimi, B.; Eslami, S. *Tetrahedron Lett.* **1999**, *40*, 4055. (f) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58. (g) Karimi, B.; Seradj, H. *Synlett* **2001**, 519.

(6) Karimi, B.; Golshani, B. *J. Org. Chem.* **2000**, *65*, 7228.