5.05 (d, 1, J = 5 Hz, H-3), 2.26 (s, 3, CH_3CO), 1.46 and 1.38 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 57.64; H, 4.90; N, 8.38; S, 9.74.

N-Acetyl-3-phthalimido-4-(2′-keto-1′-propylthio)azetidin-2-one (7).—A suspension of 60 mg of **6a** in 1 ml of acetic anhydride and 0.5 ml of pyridine was stirred at 52° for 16 hr. The resulting light-brown solution was concentrated at 0.5 mm to an oil which was chromatographed on 15 g of Florisil. After the column was washed with 125 ml of methylene chloride, the product was eluted with 250 ml of 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil which crystallized from methylene chloride–hexane to give 30 mg (44%) of delicate crystals: mp 181–182°; $[\alpha]^{23}D$ −77° (c 1.1, $CHCl_3$); ir 1800, 1775, 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 5.73 and 5.45 (two d, 2, J = 6 Hz, H-3 and H-4), 3.73 (AB quartet, 2, J = 16 Hz, CH_2), 2.50 (s, 3, NAc), 2.23 (s, 3, CAc).

Anal. Calcd for $C_{16}H_{14}N_2O_5S$: C, 55.48; H, 4.07; N, 8.08; S, 9.25. Found: C, 55.29; H, 3.92; N, 7.98; S, 9.12.

2,2-Dimethyl-3-methoxy-6-phthalimidopenam (9a).—A solution of 250 mg (0.7 mmol) of **3** and 190 mg (0.7 mmol) of mercuric chloride in 12 ml of methanol was stirred at 52° for 16 hr. Evaporation of the solvent left an oily residue which was triturated with benzene. The benzene extracts were concentrated to an oil which was chromatographed on 20 g of Florisil. The column was washed with 650 ml of methylene chloride, and the product was eluted with 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil which crystallized from ethyl acetate–hexane to give 65 mg (28%) of long needles: mp 125–126°; $[\alpha]^{23}D$ 215° (c 1.2, $CHCl_3$); ir 1790, 1775, 1720 cm^{-1}; nmr δ 7.8 (m, 4, aryl), 5.60 and 5.40 (two d, 2, J = 4.0 Hz, H-5 and H-6), 4.97 (s, 1, H-3), 3.52 (s, 3, OCH_3), 1.64 and 1.54 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 58.00; H, 4.90; N, 8.40; S, 9.80.

3-Methyl-3-methoxy-6-phthalimidopenam (9b).—In the same manner as for **9a**, the oil from 144 mg (0.47 mmol) of **6a** and 129 mg (0.47 mmol) of mercuric chloride was chromatographed on 14 g of Florisil. After the column was washed with 125 ml of methylene chloride, the product began to elute. The solvent was changed to 9:1 methylene chloride–ethyl acetate, and evaporation left a crystalline solid. Recrystallization from ethyl acetate–hexane gave 60 mg (40%) of needles: mp 170–172°; $[\alpha]^{23}D$ 149° (c 0.91, $CHCl_3$); ir 1785, 1770, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 5.63 and 5.33 (two d, 2, J = 4 Hz, H-5 and H-6), 3.41 (AB quartet, 2, J = 10.5 Hz, CH_2), 3.36 (s, 3, OCH_3), 1.96 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.69; H, 4.43; N, 8.79; S, 10.07. Found: C, 56.29; H, 4.34; N, 8.57; S, 10.31.

2,3-Dimethyl-3-methoxy-6-phthalimidopenam (9c).—In the same manner as for **9a**, the oil from 134 mg (0.42 mmol) of **6b** and 115 mg (0.42 mmol) of mercuric chloride was chromatographed on 13 g of Florisil. After the column was washed with 110 ml of methylene chloride, the product began to elute. The solvent was changed to 9:1 methylene chloride–ethyl acetate, and the product was obtained as an oil which crystallized from ethyl acetate–hexane to give 23 mg (16%) of needles: mp 130–131°; $[\alpha]^{23}D$ 191° (c 1.1, $CHCl_3$); ir 1785, 1770, and 1720 cm^{-1}; nmr δ 7.8 (m, 4, aryl), 5.57 and 5.25 (two d, 2, J = 4 Hz, H-5 and H-6), 4.06 (q, 1, J = 7 Hz, H-2), 3.36 (s, 3, OCH_3), 1.83 (s, 3, C_3 CH_3), 1.32 (d, 3, J = 7 Hz, C_2 CH_3).

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 57.55; H, 4.85; N, 8.17; S, 9.77.

Acknowledgment.—We wish to thank the Sloan Basic Research Fund No. 27609 for support of this work. J. U. P. acknowledges partial support by Simmons College for a leave of absence.

Registry No.—**1**, 41189-52-0; **2** open form, 41189-53-1; ring form, 41189-54-2; **3** open form, 41189-55-3; **3** ring form, 41189-56-4; **4a**, 41189-57-5; **4b**, 41189-58-6; **6a**, 41189-59-7; **6b**, 41189-60-0; **6c**, 41189-61-1; **7**, 41189-62-2; **9a**, 41189-63-3; **9b**, 41189-64-4; **9c**, 41189-65-5; 3-phthalimido-4-(2′-hydroxy-1′,1′-dimethylethylthio)azetidin-2-one, 41189-66-6; *N*-trifluoroacetyl-3-phthalimido-4-(2′-trifluoroacetoxy-1′,1′-dimethylethylthio)azetidin-2-one, 41189-67-7; acetone, 67-64-1; 2-butanone, 78-93-3; 3-methyl-2-butanone, 563-80-4.

Benzimidazoles from Preformed Imidazoles. A Novel Approach

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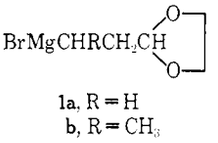
Benzimidazole derivatives **5a–e** are prepared in a two-step procedure by successive reactions of readily available imidazole-5-carboxaldehydes with reagents $BrMgCHRCH_2CHOCH_2CH_2O$ (R = H, CH_3) and cyclization of the resulting carbinols **3a–e** under controlled conditions. Alcohol $ArCHOHCH_2CH_2CHOCH_2CH_2O$ (Ar = 1-benzyl-2-methyl-5-imidazolyl) has been oxidized (MnO_2) to the ketone; addition of Grignard reagents thereto and ring closure of the new carbinols to compounds **9** and **10** illustrates a general preparation of 7-substituted benzimidazoles.

Benzimidazoles are traditionally synthesized by ultimate construction of the imidazole moiety, whereby the prerequisite *o*-phenylenediamines are cyclized with carboxylic acids and/or derivatives thereof. An alternative assembly, commencing with preformed and suitably functionalized imidazoles, has, to the best of our knowledge, hitherto escaped attention. Such an approach is herewith illustrated. It is, by its nature, complementary to existing methods, thereby allowing entry into systems otherwise found to be difficultly accessible.

In a recent[1] report concerning the hydroxymethylation of 1,2-disubstituted imidazoles, the preparation of the imidazolyl-5-methanols and 4,5-dimethanols was described. The reaction, carried out in refluxing aqueous CH_2O, proved to be pH sensitive and produced satisfactory results only in buffered (NaOAc–AcOH) milieu. Subsequent oxidation [$Pb(OAc)_4$] of the products to the aldehydes proceeded cleanly, thus providing an efficient and cheap two-step route to many imidazole-5-carboxaldehydes.

Grignard reagents **1a** and **1b** have, since 1969, found application in the synthesis of (±)-nuciferal[2]

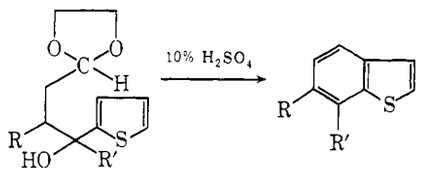


1a, R = H
b, R = CH_3

(1) E. F. Godefroi, H. J. J. Loozen, and J. Th. J. Luderer-Platje, *Recl. Trav. Chim. Pays-Bas*, **91**, 1383 (1972).

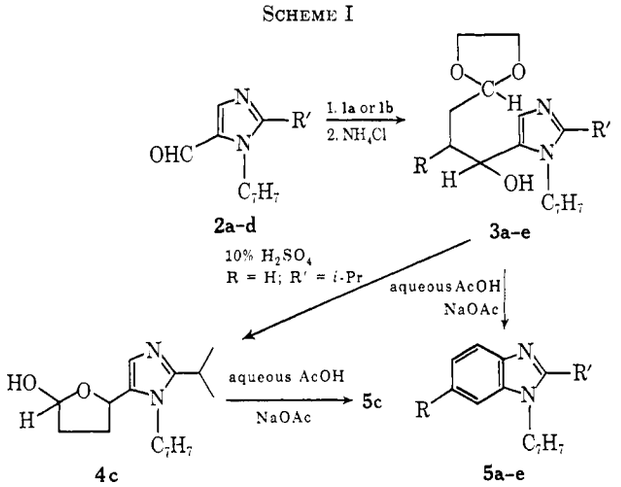
(2) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1122 (1969).

and in a general preparation of benzo[*b*]thiophenes.[3] In the present work, **1a** was allowed to react with imidazole-5-carboxaldehydes **2a–d**[1] in tetrahydrofuran, furnishing in good yields alcohols **3a–d**; similar treatment of **2b** with **1b** gave **3e**. Compound **3c** was chosen as a protoype in establishing conditions required for benzimidazole formation. Refluxing of **3c** in 10% H_2SO_4 resulted in removal of the acetal group, thereby furnishing hemiacetal **4c**. This is not surprising. Whereas these conditions had been effective in bringing about ring closure in related thiophene systems,[3] such pronounced acidic circumstances



will protonate the more basic imidazoles, thus inactivating them toward electrophilic processes. Treatment, however, of **3a–e** with refluxing NaOAc–AcOH buffer solution did produce benzimidazoles **5a–e**. Such conditions also sufficed for converting **4c** to **5c** (Scheme I).

SCHEME I



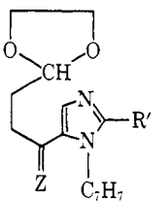
2a-d **3a-e** **4c** **5a-e**

a, R = H; R′ = CH_3
b, R = H; R′ = C_2H_5
c, R = H; R′ = i-C_3H_7
d, R = H; R′ = t-C_4H_9
e, R = CH_3; R′ = C_2H_5; C_7H_7 = benzyl

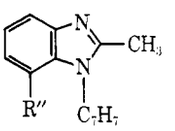
The method also proved to be of value in preparing 7-substituted benzimidazoles, as the following examples indicate. Oxidation (MnO_2–$CHCl_3$) of alcohols **3a** and **3c** produced ketones **6a** and **6b**. Of these, **6a** was treated with methyl- and isopropylmagnesium halides; the resulting tertiary alcohols (**7a** and **8a**) cyclized smoothly and provided benzimidazoles **9** and **10**.

Related reactions were found to be of particular value in gaining entry into di- and tetrahydrobenzimidazoles. To this end ketones **6a** and **6b** were reduced under Wolff–Kishner conditions to methylene derivatives **11a** and **11b**. Cyclizations were, in both cases, conducted in refluxing NaOAc–AcOH buffer (15 hr), whereby tetrahydro-4-hydroxybenzimidazoles **12a** and

(3) H. J. J. Loozen and E. F. Godefroi, *J. Org. Chem.*, **38**, 1056 (1973).

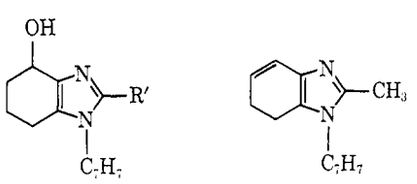


6a, R′ = CH_3; Z = O
b, R′ = i-C_3H_7; Z = O
7a, R′ = CH_3; Z = (CH_3)(OH)
8a, R′ = CH_3; Z = (i-C_3H_7)(OH)
11a, R′ = CH_3; Z = (H)(H)
b, R′ = i-C_3H_7; Z = (H)(H)



9, R″ = CH_3
10, R″ = i-C_3H_7; C_7H_7 = benzyl

12b were produced in moderate yields. Moreover, from the reaction mixture arising from **11a** a second component was isolated by column chromatography. Nmr spectra (see Experimental Section) and analytical data left no doubt as to its being **13**. Utilization of



12a, R′ = CH_3
b, R′ = i-C_3H_7

13

this approach into partially hydrogenated benzimidazoles is presently under investigation.

Experimental Section

General.—Melting points were determined on a Fisher-Johns block and are uncorrected. Nmr spectra (Varian A-60, TMS as internal standard) and ir data (Perkin Elmer 337) were consistent with assigned structures. Microanalyses were performed by Messrs. P. van den Bosch and H. Eding from our laboratories.

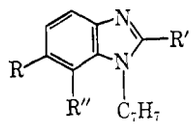
Starting Materials.—Grignard reagents **1a**, **1b**, and imidazole-5-carboxaldehydes **2a–c** were prepared as reported.[1] Aldehyde **2d** was obtained analogously (a) from 1-benzyl-2-*tert*-butylimidazole[1] to the 5-hydroxymethyl derivative (aqueous CH_2O, AcOH, NaOAc; 16-hr reflux; 47%), mp [EtOH–(i-Pr)$_2$O] 183–184°; (b) from oxidation [$Pb(OAc)_4$–pyridine] of the carbinol to **2d** (43%), mp [$CHCl_3$–(i-Pr)$_2$O] 181–182°, nmr ($CDCl_3$) δ 9.28 (s, 1, CHO).

All benzimidazoles and their open-chained precursors have been compiled in Tables I and II, respectively. Experimental details for preparing **3b** and **5b** are given.

1-(1,3-Dioxolan-2-yl)-3-hydroxy-3(1-benzyl-2-ethylimidazol-5-yl)propane (3b).—To a THF solution of **1a**, prepared from 5.0 g (0.026 mol) of the bromide[2] and 0.65 g (0.026 g-atom) of Mg was introduced slowly and with stirring at 30–35° 4.0 g (0.019 mol) of **2b** in 10 ml of THF. After 5 hr the mixture was poured onto 10% NH_4Cl solution. Extraction of the product into $CHCl_3$ and washing, drying, and stripping of solvent left a viscous oil which crystallized on addition of (i-Pr)$_2$O: yield 4.1 g (85%); mp [EtOH–(i-Pr)$_2$O] 88–89°; nmr ($CDCl_3$) δ 4.38 (t, 1, CHOH).

1-Benzyl-2-ethylbenzimidazole (5b).—Compound **3b**, 2.0 g (0.006 mol), in a solution of 6 ml of AcOH, 8 g of NaOAc, and 50 ml of H_2O, was refluxed for 16 hr. The solution was rendered basic (NaOH) and the product was extracted into $CHCl_3$. Drying and solvent removal left 1.1 g (70%) of essentially pure, oily product: nmr ($CDCl_3$) δ 1.30 (t, 3, CH_3), 2.70 (q, 2,

TABLE I



Compd	Yield,[a] %	Mp, °C	Derivative	Mp, °C	Empirical formula[e]
5a[c]	77		Picrate	185–189	$C_{15}H_{14}N_2$
5b[d]	70		Picrate	178–180	$C_{16}H_{16}N_2$
5c	92		Picrate	177–178	$C_{17}H_{18}N_2$
5d[b]	33	163–165			$C_{18}H_{20}N_2$
5e	94		Picrate	208–209	$C_{17}H_{18}N_2$
9	75	68–72	Picrate	218–219	$C_{16}H_{16}N_2$
10	62	128–129			$C_{18}H_{20}N_2$

[a] Yields are based on crude product of more than 95% purity (nmr). [b] Crude product chromatographed over silica. [c] N. S. Koslov and M. N. Stepanova, *Dokl. Akad. Nauk Beloruss. SSR*, B(6), 541 (1969); *Chem. Abstr.*, **71**, 124337a (1969). [d] K. Kondal Reddy, N. V. Subba Rao, and C. V. Ratna, *Indian J. Chem.*, **1**, 96 (1963). [e] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds in the table.

CH_2CH_3), 5.08 (s, 2, $CH_2C_6H_5$), 7.52 (m, 1, H-4 proton), 6.62–7.20 (m, 8, remaining aromatic protons).

4-Hydroxy-4-(1-benzyl-2-isopropylimidazol-5-yl)butyraldehyde (as Hemiacetal 4c).—A solution of 1.0 g (0.003 mol) of **3c** in 10 ml of 10% H_2SO_4 was refluxed for 40 min. The solution was rendered alkaline and was extracted with $CHCl_3$. Drying, solvent evaporation, and trituration of the residual oil with $(i\text{-Pr})_2O$ gave 0.650 g of product: mp 138–139°; ir (KBr) 3000–3500 cm^{-1} (OH), no C=O absorption.

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.60; H, 7.69; N, 9.79. Found: C, 71.33; H, 7.68; N, 9.59.

Refluxing of 0.5 g of **4c** in a buffer consisting of 2 g of NaOAc, 2 ml of AcOH, and 15 ml of H_2O and isolation of the product as for **5b** gave 0.3 g of an oil, spectrally (nmr) indentical with **5c**.

1-(1,3-Dioxolan-2-yl)-3-oxo-3-(1-benzyl-2-methylimidazole-5-yl)propane (6a).—A mixture of 32 g (0.11 mol) of **3a**, 150 g of activated MnO_2,[4] and 300 ml of C_6H_6 was stirred and monitored (tlc) for 24 hr. Removal of MnO_2 and solvent evaporation left 26 g (81%) of essentially pure, oily **6a**: nmr ($CDCl_3$) δ 2.30 (s, 3, CH_3), 3.74 (m, 4, dioxolane protons), 5.47 (s, 2, $CH_2C_6H_5$), 7.62 (s, 1, imidazole, 4 H); ir (Nujol) 1685 cm^{-1} (C=O), no OH absorption.

Compound 6b, the isopropyl analog of **6a**, was prepared analogously. The ketone, an oil, was characterized *via* the oxime, mp 184–185°.

Anal. Calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.45; H, 7.42; N, 12.49.

1-(1,3-Dioxolan-2-yl)-3-hydroxy-3-(1-benzyl-2-methylimidazol-5-yl)butane (7a).—Dropwise addition of 6.0 g (0.02 mol) of crude **6a** to 20 ml of 1 *M* MeMgI in Et_2O and customary work-up of the mixture after 2 hr with 10% NH_4Cl afforded an oil. This was triturated with $(i\text{-Pr})_2O$ to give 3.2 g (51%) of **7a**, mp 115–118°.

1-(1,3-Dioxolan-2-yl)-3-(1-benzyl-2-methylimidazol-5-yl)propane (11a).—To a solution of 20 g (0.066 mol) of **6a** in 150 ml of diethylene glycol was added 15 g of powered KOH and 10 ml of $N_2H_4 \cdot H_2O$. The mixture was refluxed for 1 hr, whereupon solvent was removed until the internal temperature had reached 200°. Hereupon heating was continued for an additional 5 hr. The reaction was quenched by addition to water from which the product was isolated by ether extraction. Drying and solvent removal then left crude, oily product, which, on distillation gave 13.2 g (70%) of product: bp 170–180° (0.02 mm); nmr ($CDCl_3$) δ 2.28 (s, 3, CH_3), 3.03 (m, 4, dioxolane protons), 5.01 (s, 2, $CH_2C_6H_5$), 6.74 (s, 1, imidazole 4 H), 6.80–7.40 (m, 5, C_6H_5); ir no C=O.

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 72.19; H, 7.87; N, 10.38.

Compound 11b, bp 180–184° (0.03 mm), was similarly prepared from **6b**. It solidified on standing; analytical material [petroleum ether (bp 30–60°)] had mp 57–58°.

Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.48; H, 8.08; N, 8.83.

1-Benzyl-2-isopropyl-4-hydroxy-4,5,6,7-tetrahydrobenzimidazole (12b).—A solution of 1.0 g (0.0034 mol) of **11b**, 4 g of NaOAc, and 3 ml of AcOH in 20 ml of H_2O was refluxed for 12 hr. The solution was rendered alkaline and the resulting oil was taken up in Et_2O. Drying and evaporation of the organic phase left an oil, which, on addition of $(i\text{-Pr})_2O$ surrendered 0.35 g (40%) of product: mp (C_6H_6–petroleum ether) 147–149°; nmr ($CDCl_3$) δ 1.26 (d, 6, CH_3), 4.41 (s, 1, OH), 5.02 [m, 1, CH(OH)], 5.13 (s, 2, CH_2Ar).

Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.51; H, 8.16; N, 10.89.

Reaction of 11a in Refluxing Aqueous NaOAc–AcOH.—Treatment of 2.0 g (0.0071 mol) of **11a** in a refluxing solution of 8 g of NaOAc and 6 ml of AcOH in 40 ml of H_2O for 12 hr and work-up of the mixture as described for **12b** gave 0.42 g (25%) of **12a**, mp 165–169°.

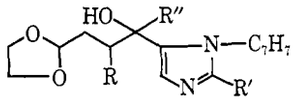
Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.33; H, 74.37; N, 11.38.

Column chromatography of the mother liquors of **12a**, using 2% MeOH in $CHCl_3$ as eluent, provided *ca.* 0.10 g of dihydrobenzimidazole **13**: nmr ($CDCl_3$) δ 2.28 (s, 3, CH_3), 4.95 (s, 2, $CH_2C_6H_5$), 6.45 (d, 1, olefin H_4), 5.56 (m, 1, olefin H_5), 6.90–7.45 (m, 5, C_6H_5).

The picrate salt, prepared in the usual way, had mp 148–152°.

Anal. Calcd for $C_{13}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 55.63; H, 4.22; N, 15.45. Found: C, 55.44; H, 4.41; N, 15.44.

TABLE II



Compd	Yield,[a] %	Mp, °C	Empirical formula[c]
3a	66	108–110	$C_{17}H_{22}N_2O_3$
3b	85	88–89	$C_{18}H_{24}N_2O_3$
3c	68	90–91	$C_{19}H_{26}N_2O_3$
3d	79	138–140	$C_{20}H_{28}N_2O_3$
3e	80	197–99	$C_{19}H_{26}N_2O_3$
7a	51	118–120	$C_{18}H_{24}N_2O_3$
8a[b]	61	159–161	$C_{20}H_{28}N_2O_3$

[a] Yields based on crude, triturated ($i\text{-Pr}_2O$) products of more than 95% purity (nmr). [b] Prepared analogously to **7a** (see Experimental Section). [c] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds in the table.

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Registry No.—**2a**, 39269-74-4; **2b**, 39269-75-5; **2c**, 39269-79-9; **2d**, 41030-00-6; **3a**, 41030-01-7; **3b**, 41030-02-8; **3c**, 41030-03-9; **3d**, 41030-04-0; **3e**, 41030-05-1; **4c**, 41030-06-2; **5a**, 5805-83-4; **5a** picrate, 24103-24-0; **5b**, 23982-79-8; **5b** picrate, 24107-49-1; **5c**, 41030-11-9; **5c** picrate, 41030-12-0; **5d**, 41030-13-1; **5e**, 41030-14-2; **5c** picrate, 41030-15-3; **6a**, 41030-16-4; **6b**, 41030-17-5; **6b** oxime, 41030-18-6; **7a**, 41030-19-7; **8a**, 41030-20-0; **9**, 41030-21-1; **9** picrate, 41030-22-2; **10**, 41030-23-3; **11a**, 41030-24-4; **11b**, 41030-25-5; **12a**, 41047-21-6; **12b**, 41030-26-6; **13**, 41030-27-7; **13** picrate, 41030-28-8; 1-(1,3-dioxolan-2-yl)-2-bromoethane, 18742-02-4.

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