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An exception to the normal Mitsunobu reaction with phenols; the formation of hydrazones from salicylaldehydes

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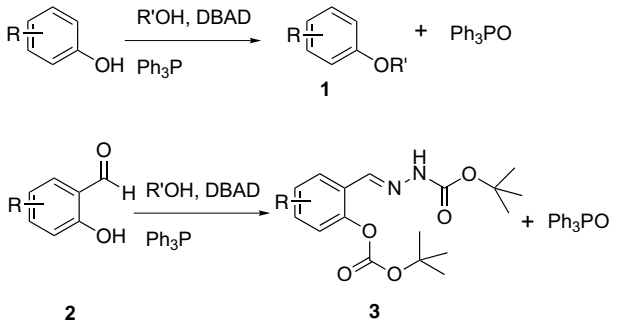
Abstract—The reaction of 2-hydroxybenzaldehydes with alkanols in the presence of triphenylphosphine and di-*tert*-butyl azodicarboxylate (DBAD), under the Mitsunobu reaction conditions, gives rise to the formation of hydrazones as the major products rather than the expected alkyl aryl ethers.

The reaction of alcohols with acidic compounds ($pK_a \leqslant 11$) in the presence of triphenylphosphine and a dialkyl azodicarboxylate (the Mitsunobu reaction) has become widely used for the functionalization of alcohols and related compounds.[1] For example, the reaction of alkanols with phenols, discovered by Bittner and Assaf[2] and Manhas et al.,[3] afforded the corresponding alkyl aryl ethers **1** (Scheme 1). However, we wish to report herein that the expected alkyl aryl ethers are not produced, or are obtained only as minor products, when the phenol is substituted in its *ortho* position by a formyl group. Instead, hydrazones **3** are obtained as the major products. These hydrazones, which might be useful precursors for the preparation of heterocycles,[4] are also prepared in the absence of alkanol, and their structure was unequivocally established from the X-ray crystallographic analysis of the 3,5-dichloro derivative **3f** (Fig. 1).[5]



Scheme 1.

In order to explore the scope of this new reaction and to gain insight into its mechanism, a series of commercially available 2-hydroxybenzaldehydes (salicylaldehydes) were reacted with triphenylphosphine and DBAD and the results are summarized in Table 1.[6] Although the use of diethyl azodicarboxylate or bis(2,2,2-trichloroethyl) azodicarboxylate gave the corresponding hydrazones, albeit in lower yield with the second reagent, we selected DBAD as the reagent of choice. It is a stable, commercially available, crystalline yellow solid and the *tert*-butoxycarbonyl (BOC) group is widely used as a protecting group due to its ease of removal under mild conditions. Both electron-rich salicylaldehydes (**2d**, **e**) and electron-poor substrates (**2f**, **g**) gave excellent yields of hydrazones **3**, and various substitution patterns were well tolerated. The same major product was also obtained in the presence of an alkanol (entries a, e and h), showing that the Mitsunobu reaction does not occur as the major pathway. We have also observed that this reaction is specific to salicylaldehydes. Under the same experimental conditions, the application of this method to *p*- and *m*-hydroxybenzaldehydes did not provide the corresponding hydrazones.

When a second hydroxyl group is present on the aromatic ring, up to 2 equiv of DBAD and Ph_3P are required (Table 1, salicylaldehydes **2j–l**). In these cases

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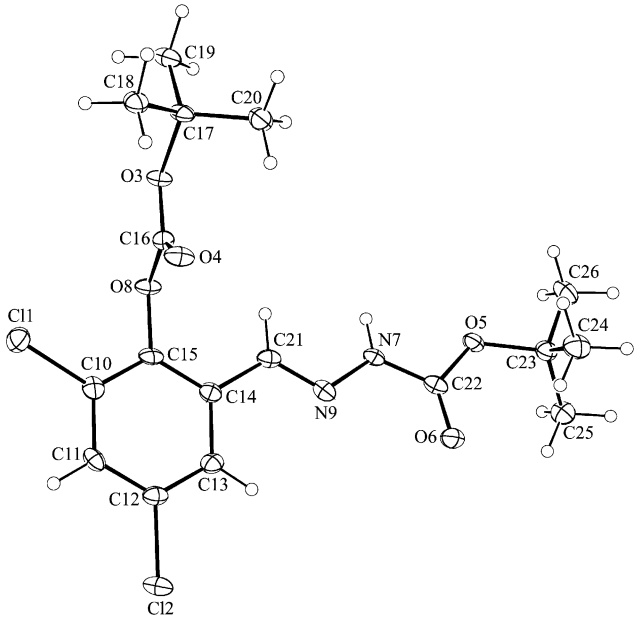
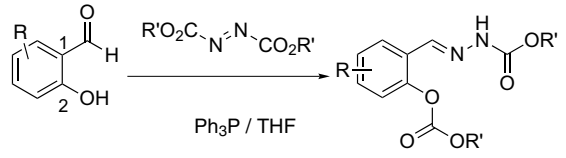


Figure 1. ORTEP representation of **3f**.

Table 1. Reaction of salicylaldehydes, with triphenylphosphine and dialkyl azodicarboxylates



2a-l **3a-l**

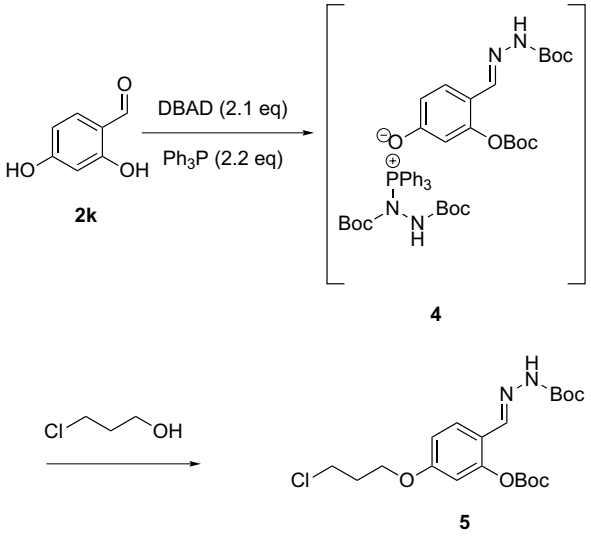
2	R	R′	Yield (%)	Mp (°C)
a	H	*t*-Bu	84 (80)[e]	139–140
b	H	Et	84	93–94
c	H	Cl_3CCH_2	54	73–74
d	6-MeO	*t*-Bu	79	85–86
e	4-MeO	*t*-Bu	81 (62)[e,f]	146–147
f	3,5-Cl_2	*t*-Bu	82	155–156
g	5-Br	*t*-Bu	86	122–123
h	6-Br, 3-MeO	*t*-Bu	77 (75)[e]	123–124
i	3,4-CHCHCHCH–[a]	*t*-Bu	90	183–184
j	3-OH[b]	*t*-Bu	70	114–115
k	5-OH[c]	*t*-Bu	79	139–140
l	4-OH[d]	*t*-Bu	79	120–122

[a] 1-OH-2-Naphthaldehyde.
[b] 1.7 equiv of DBAD and Ph_3P; pK_a of 3-hydroxyl substituent: 11.8.
[c] 1.8 equiv of DBAD and Ph_3P; pK_a of 5-hydroxyl substituent: 10.9.
[d] 2 equiv of DBAD and Ph_3P; pK_a of 4-hydroxyl substituent: 7.5.
[e] Reaction performed in the presence of 1 equiv of 3-chloro-l-propanol.
[f] The Mitsunobu product **8** was also obtained in 22% yield.

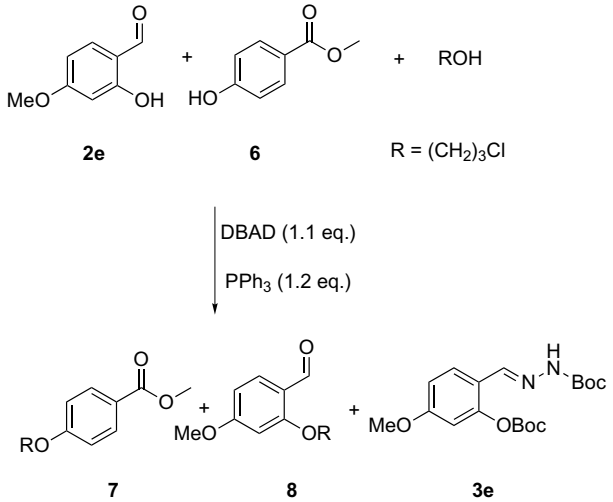
the amount needed for complete consumption of the hydroxy salicylaldehyde depends on the pK_a of the other OH (R) (their relative acidities have been evaluated using computational methods). This group acts as a scavenger for the Ph_3P/DBAD complex **9**[1] (vide supra, Scheme 4). With the more acidic hydroxyl, 2 equiv of reagents are needed to produce the phosphonium/phenolate **4**. Interestingly, upon subsequent addition of 1 equiv of an alkanol, the alkylation product **5** can be generated as the major compound (Scheme 2).

In order to determine whether hydrazone formation is faster than the usual Mitsunobu reaction on the hydroxyl group, the competition experiment described in Scheme 3, with the phenols **2e** and **6** (having similar calculated pK_a values) was carried out. In this case, the hydrazone **3e** and alkylation product **7**[7] were obtained in a 1:1 ratio, suggesting the rate of these two pathways to be quite similar. Thus, under certain conditions, the Mitsunobu reaction competes with the formation of hydrazone.

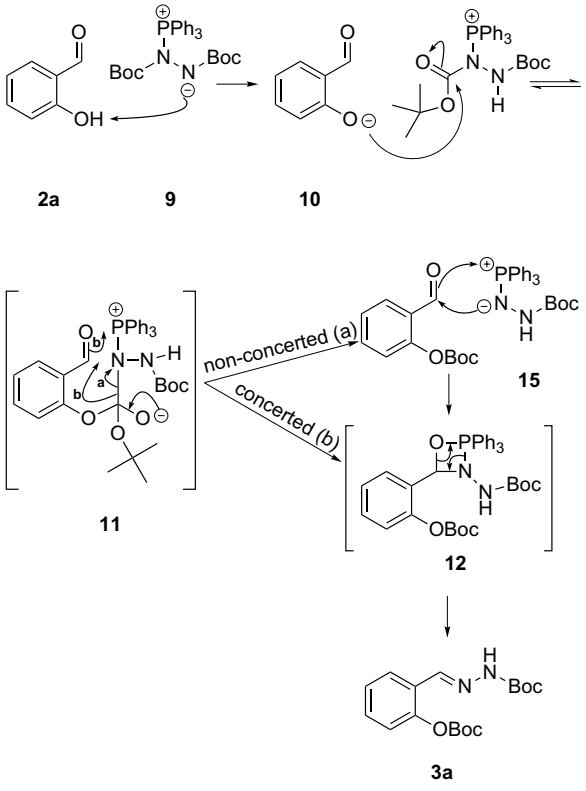
To explain that the hydroxyl in the 2-position is necessary for hydrazone formation, we propose the following mechanism (Scheme 4). Triphenylphosphine and DBAD react together to give the salt **9**. The phenolate **10** is then



Scheme 2.



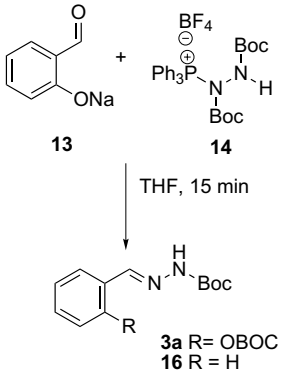
Scheme 3.



Scheme 4. Proposed mechanism.

produced by the reaction of salt **9** with 2-hydroxybenzaldehyde. We speculate that alkoxide **11**, generated from the phenolate **10**, can be converted via an aza-Wittig reaction in a concerted or non-concerted fashion, to oxazaphosphetane **12**. Further loss of Ph_3PO, which is the driving force of the reaction, yields hydrazone **3a**.

To validate the above-mentioned mechanism, various experiments were carried out. Initially, we assumed that the anion of salicylaldehyde is obtained. The successful formation of hydrazone **3a** (80% yield) from the reaction of the sodium salt of salicylaldehyde **13**[8] and the tetrafluoroborate salt **14**[9] confirms this assumption (Scheme 5). Under the same condition, but using salicylaldehyde **2a** instead of its sodium salt **13**, the hydrazone **3a** is not obtained.



Scheme 5.

We believe that the reaction proceeds via a concerted mechanism. If the mechanism was non-concerted, the aza-ylide intermediate **15** (Scheme 4) produced in the reaction mixture might react intermolecularly with benzaldehyde to produce compound **16**.[10] However, reaction of the sodium salt of salicylaldehyde **13**, benzaldehyde and the BF_4 salt **14** did not give a detectable amount of compound **16** and yielded compound **3a** as the only product (Scheme 5).

In conclusion, we have demonstrated that hydrazones are produced in high yields from the reaction of salicylaldehyde with triphenylphosphine and DBAD. The same compounds are obtained in the presence of alkanols, instead of the normal expected aryl alkyl ether, which are not detected or obtained only as minor products. We are currently expanding this approach to *o*-amino and *o*-mercaptobenzaldehydes, and those results will be reported in due course.

Acknowledgements

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4. Unsubstituted and N-substituted hydrazones have been used in the preparation of heterocycles: Katritzky, A. R.; Rees, C. W. In *Comprehensive Heterocyclic Chemistry*; Pergamon, 1984; Vol. 3, p 41; Vol. 4, pp 334, 337; Vol. 7, p 75 and references cited therein. They are most often synthesized from alkyl hydrazine and an appropriate aldehyde or ketone.[11]
5. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 256969. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 0 1223 336033. E-mail: deposit@ccdc.cam.ac.uk].
6. Standard experimental procedure: the salicylaldehyde dissolved in THF (0.35 M) was added to di-*tert*-butyl azodicarboxylate (1.1 equiv) and triphenylphosphine (1.2 equiv). After 15 min, the reaction was quenched with satd aqueous NH_4Cl and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The product was purified by flash chromatography and triturated in hexane. Spectral data are given below.
Compound **3a**: ^1H NMR (400 MHz, acetone-d_6): δ 9.98 (s, 1H), 8.27 (s, 1H), 7.99 (dd, J = 7.82, 1.41 Hz, 1H), 7.44 (t, J = 7.74 Hz, 1H), 7.33 (t, J = 7.53 Hz, 1H), 7.21 (d, J = 7.79 Hz, 1H), 1.54 (s, 9H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6): δ 152.7, 151.8, 149.8, 137.5, 130.5, 127.9, 126.5, 126.5, 123.1, 83.6, 80.1, 28.2, 27.1. HRMS: MK^+ 375.1320 (expected 375.1322).
Compound **3b**: ^1H NMR (400 MHz, acetone-d_6): δ 10.1 (s, 1H), 8.26 (s, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.47 (t,

J = 7.7 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.21 (q, J = 6.9 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H). HRMS: MH^+ 281.1137 (expected 281.1138).

Compound **3c**: ^{1}H NMR (400 MHz, acetone-d_6): δ 10.73 (s, 1H), 8.37 (s, 1H), 7.93 (br s, J = 5.8 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 5.09 (s, 2H), 4.97 (s, 2H). HRMS: MH^+ 484.8801 (expected 484.8800).

Compound **3d**: ^{1}H NMR (400 MHz, acetone-d_6): δ 9.71 (s, 1H), 8.34 (s, 1H), 7.36 (t, J = 8.3 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 3.90 (s, 3H), 1.52 (s, 9H), 1.50 (s, 9H). HRMS: MH^+ 367.1869 (expected 367.1870).

Compound **3e**: ^{1}H NMR (400 MHz, acetone-d_6): δ 9.82 (s, 1H), 8.17 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 6.93 (dd, J = 8.8, 2.3 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 3.87 (s, 3H), 1.54 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6): δ 161.9, 152.7, 151.6, 150.9, 137.7, 127.5, 120.5, 113.0, 108.2, 83.6, 79.8, 55.6, 30.0, 28.8. HRMS: MK^+ 405.1423 (expected 405.1423).

Compound **3f**: ^{1}H NMR (400 MHz, acetone-d_6): δ 10.19 (s, 1H), 8.22 (s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 2.5 Hz, 1H), 1.55 (s, 9H), 1.51 (s, 9H). Elemental analysis: $C_{17}H_{22}Cl_2N_2O_5$: calcd: C, 50.38; H, 5.47; N, 6.91; found: C, 50.49; H, 5.53; N, 6.84.

Compound **3g**: ^{1}H NMR (400 MHz, acetone-d_6): δ 10.11 (s, 1H), 8.21 (s, 1H), 8.12 (br s, 1H), 7.59 (dd, J = 8.6, 2.3 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 1.54 (s, 9H), 1.51 (s, 9H). Elemental analysis: $C_{17}H_{23}BrN_2O_5$: calcd: C, 49.17; H, 5.58; N, 6.75; found: C, 49.55; H, 5.64; N, 6.68.

Compound **3h**: ^{1}H NMR (400 MHz, acetone-d_6): δ 10.02 (s, 1H), 8.28 (s, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 8.9 Hz, 1H), 3.89 (s, 3H), 1.53 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6): δ 152.6, 152.1, 150.8, 140.0, 139.5, 130.8, 128.2, 114.5, 113.7, 82.9, 80.0, 56.3, 28.0, 27.3. HRMS: MK^+ 483.0534 (expected 483.0533).

Compound **3i**: ^{1}H NMR (400 MHz, acetone-d_6): δ 10.09 (s, 1H), 8.46 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 6.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.65–7.59 (m, 2H), 1.58 (s, 9H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6): δ 153.1, 151.9, 145.4, 137.9, 135.1, 129.1, 128.5, 128.3, 127.6, 127.3, 124.7, 122.8, 121.6, 85.0, 80.6, 28.9, 28.1. Elemental analysis: $C_{21}H_{26}N_2O_5$: calcd: C, 65.27; H, 6.78; N, 7.25; found: C, 64.93; H, 7.01; N, 7.34.

Compound **3j** ^{1}H NMR (400 MHz, acetone-d_6): δ 11.74 (s, 1H), 10.24 (s, 1H), 8.29 (s, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.92 (t, J = 7.9 Hz, 1H), 1.54 (s, 9H), 1.52 (s, 9H). HRMS: MH^+ 353.1713 (expected 353.1713).

Compound **3k**: ^{1}H NMR (400 MHz, acetone-d_6): δ 9.97 (s, 1H), 8.51 (s, 1H), 8.17 (s, 1H), 7.45 (d, J = 2.9 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.88 (dd, J = 8.8, 3.0 Hz, 1H), 1.52 (s, 9H), 1.5 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 152.6, 152.3, 143.0, 137.4, 128.5, 123.9, 117.7, 111.6, 83.2, 80.1, 28.0, 27.3. HRMS: MK^+ 391.1270 (expected 391.1272).

Compound **3l**: ^{1}H NMR (400 MHz, acetone-d_6): δ 9.78 (s, 1H), 8.99 (s, 1H), 8.15 (s, 1H), 7.84 (d, J = 8.7 Hz, 1H), 6.83 (dd, J = 8.7, 2.3 Hz, 1H), 6.68 (d, J = 2.3 Hz, 1H), 1.53 (s, 9H), 1.49 (s, 9H). HRMS: MH^+ 353.1713 (expected 353.1713).

Compound **5**: ^{1}H NMR (400 MHz, acetone-d_6): δ 9.83 (s, 1H), 8.18 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.7, 2.2 Hz, 1H), 6.83 (d, J = 2.2 Hz, 1H), 4.22 (t, J = 5.9 Hz, 2H), 3.83 (t, J = 6.4 Hz, 2H), 2.31–2.25 (m, 2H), 1.54 (s, 9H), 1.50 (s, 9H). HRMS: MK^+ 467.1353 (expected 467.1351).

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