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# Novel synthesis of α-diazoketones from acyloxyphosphonium salts and diazomethane

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**Abstract**—A novel, simple and mild method to prepare α-diazoketones from carboxylic acids is presented. The procedure involves the reaction of carboxylic acids with triphenylphosphine/NBS and subsequent treatment with diazomethane. $^{13}C$ and $^{31}P$ NMR experiments demonstrate that the process occurs through an acyloxyphosphonium salt as a key intermediate. 

There has been a recent resurgence of interest in the diazo moiety, especially that found in α-diazo carbonyl compounds. In the presence of various transition metal derived catalysts, α-diazocarbonyl compounds became synthetically valuable reagents in homologation reactions, insertion into X–H bonds, ylide formation, cyclopropane synthesis, etc.[1]

In connection with another project, we required a wide range of α-diazoketones derived from structurally diverse pyrrolyl- and indolylalkanoic acids. In several instances the desired compounds could not be prepared from diazomethane and the acid chlorides[2] (stability reasons), the mixed alkylcarbonic-carboxylic anhydrides,[3] acyl mesylates,[4] or any of a number of other *O*-activated carboxylic acids.[1] We were attracted by the utility of putative acyloxyphosphonium salts in the synthesis of amides,[5] esters,[6] and acyl azides,[7] and wondered if such species could also be used for the preparation of α-diazoketones. Herein is described a summary of our recent successful endeavors in this area.

Our initial optimization studies were carried out on benzoic acid. In a typical reaction sequence, a slight excess of *N*-bromosuccinimide (NBS) was added to an equimolar mixture of benzoic acid and triphenylphosphine in various solvents at 0°C. After 15 min, excess ethereal diazomethane (5 mol/mol acid) was added and the reaction mixture was worked up after an appropriate period of time. Diazoacetophenone (**2**), contaminated by small amounts of bromoacetophenone was obtained in all cases, with THF being one of the best solvents (Table 1). In contrast, when the NBS and diazomethane additions were effected at −20°C (THF), methyl benzoate was the only product.

In a second series of experiments, various co-reactants were compared with NBS (Table 2) using THF as the solvent. *N*-Chlorosuccinimide, diethyl azodicarboxylate, and carbon tetrachloride (reagent prepared at 60°C) were all inferior to NBS with regard to α-diazoketone generation. The scope of this new α-diazoketone synthesis was then examined using NBS in THF at 0°C as the preferred reaction conditions. The data in Table 3 show that the process was successful for homocyclic and heterocyclic aromatic carboxylic acids, simple aliphatic carboxylic acids, and various α-substituted acetic acid derivatives, including α-haloacetic, hippuric, and 2-pyrroleacetic acids.[8] The α-diazoketone yields are comparable or superior to those obtained by other commonly used methods. For example, Holt, et al.[25] reported that compounds **7**, **16** and **17** were obtained in ca. 50% yield from dicyclohexylcarbodiimide activated carboxylic acids.

What is the true nature of the carboxyl activated species in this reaction and perhaps in the processes referred to above? Appel,[26] and others[27] have suggested an acyl halide intermediate derived from halide attack on the acyl carbon of the acyloxyphosphonium salt.

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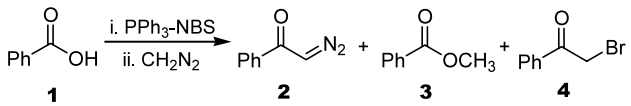
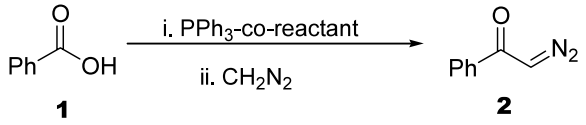
**Table 1.** Effect of solvent on diazoketone formation. Yields of **2**, **3** and **4** using $PPh_3$ (1 equiv.), NBS (1.1 equiv.), and $CH_2N_2$ (5 equiv. Ar atmosphere) and the specified solvent




| Entry | Solvent | Temperature (°C) | Yield of **2** (%) | Yield of **3** (%) | Yield of **4** (%) |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 0 | 51 | – | Traces[a] |
| 2 | Toluene | 0 | 76 | – | Traces[a] |
| 3 | $CH_2Cl_2$ | 0 | 84 | – | Traces[a] |
| 4 | THF | 0 | 87 | – | 13 |
| 5 | THF | –20 | 0 | 86 | – |

[a] Detected by thin-layer chromatography.

**Table 2.** Effect of the co-reactant on diazoketone formation

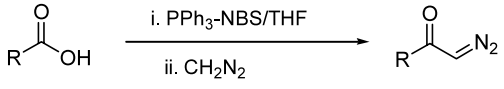



| Entry | Co-reactant | Activation temperature (°C) | Yield of **2** (%) |
|---|---|---|---|
| 1 | NBS | 0 | 87 |
| 2 | NCS | 0 | 79 |
| 3 | DEAD | 0 | 53 |
| 4 | $CCl_4$ | 60 | 43 |

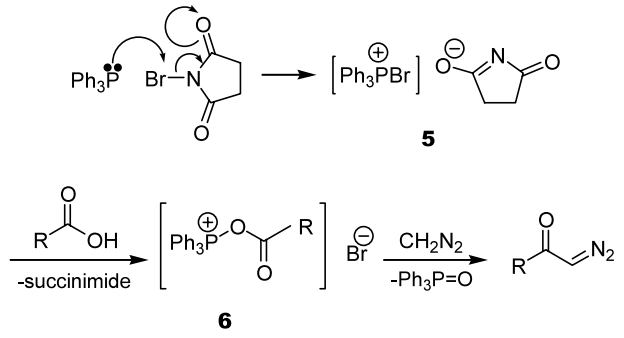
Froyen[28] has proposed that the acyloxyphosphonium salt itself is the actual reacting species. He has shown that such salts are stable at room temperature, and that the acyl halides are only formed upon heating.[28] We chose to examine the NMR spectral characteristics of the species generated under the conditions used for the α-diazoketone synthesis. The $^{31}P$ NMR spectrum of a deuteriochloroform solution of equimolar quantities of triphenylphosphine, benzoic acid and NBS, prepared at 0°C, showed a single absorption at $\delta$ 46.9. No absorptions for triphenylphosphine ($\delta$ –4.8), or triphenylphosphine oxide ($\delta$ 29.6) were present. The $^{13}C$ NMR spectrum showed, among other absorptions, two low fields signals at $\delta$ 178.1 and 171.2. The lower field signal is due to the succinimide carbonyl carbons, while the $\delta$ 171.2 signal corresponds to neither benzoic acid ($\delta$ 172.6), nor benzoyl bromide ($\delta$ 165.7). We attribute the $^{31}P$ and $^{13}C$ signals at $\delta$ 46.9 and 171.2 to the phosphorus and acyl carbon atoms of the acyloxyphosphonium salt **6**, formed as indicated in Scheme 1. It is this species which must react with diazomethane to generate the α-diazoketone.

In summary, addition of NBS to equimolar amounts of triphenylphosphine and a carboxylic acid generates an

**Table 3.** Diazoketones prepared from carboxylic acids, $PPh_3$, NBS and diazomethane




| Entry | Acid | Diazoketone | Yield (%) | Entry | Acid | Diazoketone | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5COOH$ | $C_6H_5COCHN_2$ **2**[9] | 87 | 13 | 2-$NO_2C_6H_4COOH$ | 2-$NO_2C_6H_4COCHN_2$ **18**[20] | 99 |
| 2 | 4-$ClC_6H_4COOH$ | 4-$ClC_6H_4COCHN_2$ **7**[10] | 89 | 14 | 4-$CH_3COC_6H_4CO_2H$ | 4-$CH_3COC_6H_4COCHN_2$ **19** | 97 |
| 3 | 3-$ClC_6H_4COOH$ | 3-$ClC_6H_4COCHN_2$ **8**[11] | 83 | 15 | 2-NaphthylCOOH | 2-NaphthylCOCHN$_2$ **20**[10] | 77 |
| 4 | 4-$IC_6H_4COOH$ | 4-$IC_6H_4COCHN_2$ **9**[12] | 63 | 16 | 2-FurylCOOH | 2-FurylCOCHN$_2$ **21**[21] | 53 |
| 5 | 3-$IC_6H_4COOH$ | 3-$IC_6H_4COCHN_2$ **10**[13] | 53 | 17 | 2-PyridylCOOH | 2-PyridylCOCHN$_2$ **22**[21] | 99 |
| 6 | 2-$IC_6H_4COOH$ | 2-$IC_6H_4COCHN_2$ **11**[14] | 65 | 18 | $ClCH_2COOH$ | $ClCH_2COCHN_2$ **23**[9] | 44 |
| 7 | 4-$CH_3OC_6H_4COOH$ | 4-$CH_3OC_6H_4COCHN_2$ **12**[10] | 75 | 19 | $CH_3(CH_2)_{15}CHBr$-COOH | $CH_3(CH_2)_{15}CHBr$-$COCHN_2$ **24** | 71 |
| 8 | 2-$CH_3OC_6H_4COOH$ | 2-$CH_3OC_6H_4COCHN_2$ **13**[15] | 48 | 20 | $CH_3(CH_2)_{15}COOH$ | $CH_3(CH_2)_{15}COCHN_2$ **25**[22] | 94 |
| 9 | 3-$CH_3C_6H_4COOH$ | 3-$CH_3C_6H_4COCHN_2$ **14**[16] | 44 | 21 | BzNHCH$_2$COOH | BzNHCH$_2$COCHN$_2$ **26**[23] | 69 |
| 10 | Vanillic | 3.4-$(CH_3O)_2C_6H_3COCHN_2$ **15**[17] | 29 | 22 | 1-Methyl-2-pyrroleacetic | (1-Methyl-2-pyrrolyl) $CH_2$-$COCHN_2$ **27** | 61 |
| 11 | 4-$NO_2C_6H_4COOH$ | 4-$NO_2C_6H_4COCHN_2$ **16**[18] | 98 | 23 | 3-Indoleproprionic | (3-Indolyl)$CH_2CH_2$-$COCHN_2$ **28**[24] | 91 |
| 12 | 3-$NO_2C_6H_4COOH$ | 3-$NO_2C_6H_4COCHN_2$ **17**[19] | 53 | | | | |




**Scheme 1.** Mechanism proposed for α-diazoketone formation.

acyloxyphosphonium salt, detectable by NMR spectroscopy, which reacts with diazomethane to produce an α-diazoketone. This new α-diazoketone synthesis is effected under mild conditions, has good functional group tolerance, presents some advantages in comparison with other methods and finally is broad in scope. These characteristics suggest that this route to α-diazoketones will enjoy widespread application.

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8. Typical procedure for the synthesis of diazoketones. To a solution of $PPh_3$ (1 mmol) and carboxylic acid (1 mmol) in anhydrous THF (1 mL) at 0°C, NBS (1.1 mmol) in THF (5 mL) was added dropwise over a 10 min period. The resulting reaction mixture was stirred under nitrogen atmosphere for 15 min at 0°C and the mixture was allowed to warm to room temperature continuing the stirring for an additional 15 min. The mixture was cooled to 0°C again. Then, an ether solution of diazomethane (5 mmol) from *N*-methyl-*N*-nitroso-4-toluenesulfonamide (7.15 mmol) was added. A vigorous evolution of nitrogen occurred, and the mixture was allowed to warm to room temperature overnight. The solvent was removed in vacuo and the product was purified by flash column chromatography ($SiO_2$, hexane/ethyl acetate 8:2). Selected spectral data. Compound **19**: $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.64 (s, 3H), 5.99 (s, 1H), 7.82–7.86 (d, 2H), 8.00–8.04 (d, 2H). $^{13}$C NMR: ($CDCl_3$, 75 MHz) $\delta$ 24.6, 54.9, 126.8, 128.4, 139.8, 139.9, 177.2. MS [EI+] *m*/*z* (RI%): 188 $[M]^+$ (64), 145 $[M-CH_3-N_2]^+$ (100). IR: ($CHCl_3$, $cm^{-1}$) 2112, 1701, 1624. Compound **24**: $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 0.85–0.90 (t, 3H), 1.25 (m, 30H), 4.17–4.22 (t, 1H), 5.68 (s, 1H). $^{13}$C NMR: ($CDCl_3$, 75 MHz) $\delta$ 14.0, 22.6, 27.2, 29.3, 29.9, 31.8, 34.9, 52.7, 54.8, 190.0. MS [EI+] *m*/*z* (RI%): 387 $[M]^+$ (7), 359 $[M-N_2]^+$ (2), 55 $[M-CH_3(CH_2)_{15}-Br-N_2]^+$ (100). IR: ($CHCl_3$, $cm^{-1}$) 2119, 1617. Compound **27**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.53 (s, 3H), 3.59 (s, 2H), 5.13 (s, 1H), 6.02 (m 1H), 6.07 (t, 1H, $J_{3\text{-}4}=3.5$ Hz), 6.60 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 39.4, 41.8, 52.4, 108.6, 108.7, 121.1, 121.2, 195.2; MS [EI+] *m*/*z* (RI%): 163 $[M]^+$ (77), 94 $[M-COCHN_2]^+$ (100). IR (film, $cm^{-1}$) 2105, 1738, 1637.
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