Pergamon

Tetrahedron Letters 41 (2000) 9943–9947

TETRAHEDRON
LETTERS

A new and efficient route toward the preparation of diazo ketones using cyanuric chloride and diazomethane

David C. Forbes,* Elvis J. Barrett, Derrick L. Lewis and Mary C. Smith

Department of Chemistry, University of South Alabama, Mobile, AL 36688-0002, USA

Received 9 October 2000; accepted 12 October 2000

Abstract

A new method for the preparation of diazo ketones has been developed. 2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride) has been found to be an excellent coupling reagent allowing for the efficient transfer of diazomethane to a carboxylic acid. Preparation of diazo ketones using carboxylic acids and triazine reagents is considerably more convenient than classical diazo transfer protocols because water does not have to be stringently removed and the entire procedure can be carried out in one-pot. Electron deficient and neutral aryl carboxylic acids were found to give better results than electron rich or aliphatic carboxylic acids. © 2000 Elsevier Science Ltd. All rights reserved.

Since the first recorded synthesis of an α-diazocarbonyl compound by Curtius in 1883,[1] the diazo moiety has become a key component in a number of synthetic transformations.[2] Diazocarbonyl compounds are extremely versatile and have been prominent in many catalytic carbon–carbon bond forming reactions. Most notable would be those involving cyclopropanation, cyclopropenation, aromatic cycloaddition and ylide-type transformations.[2b,3] The preparation of α-diazocarbonyl compounds can be accomplished by two main routes, derivatization of existing diazoalkanes and diazo transfer processes using a sulfonyl azide (Fig. 1).[2]

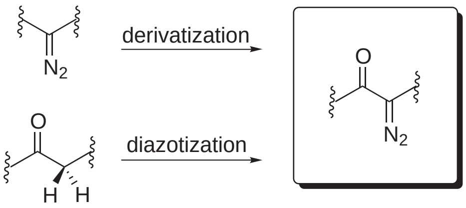


Figure 1. Strategic methods for α-diazocarbonyl preparation

---

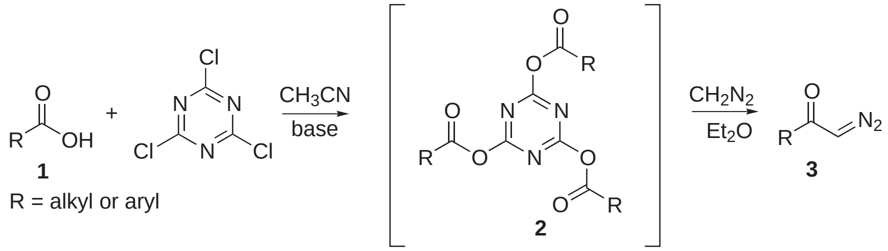
* Corresponding author. Fax: 334 460-7359; e-mail: dforbes@jaguar1.usouthal.edu

PII: S0040-4039(00)01791-3

Excluding cyclic derivatives, the most logical retrosynthetic disconnection of α-diazocarbonyl compounds involves simple acylation of diazoalkane derivatives. Indeed the most popular protocol involves the use of an acid chloride and diazomethane in excess. This route is sometimes complicated by the presence of other functional groups in the molecule and thus diazotization of the carboxylic acid via a mixed carbonic anhydride or an activated α-methylene group flanked by an additional carbonyl derivative has also been used.[2] As alternative synthetic schemes are either circuitous or mandate the exclusion of water and typically involve two or more steps using reagents of moderate to high cost, we began an investigation designed to find a more convenient synthesis of these key compounds.

2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride) has been reported as an efficient reagent in a number of coupling processes involving the preparation of amides, esters and anhydrides.[4] This cost-effective reagent is amenable to large-scale processes with the only by-product being insoluble hydroxytriazine. We have found, for the first time, that this reagent can be used in conjunction with diazomethane for the preparation of diazo ketones in one-pot without the exclusion of water. The need to either use or prepare moisture sensitive and perhaps expensive compounds is completely circumvented with this new synthetic method.

Our investigation into the use of cyanuric chloride began when we found that classical acid chloride and diazomethane protocols were unsuitable for the synthesis of a number of functionalized diazo ketones. Although the yields were modest, we were delighted to observe the feasibility of diazo ketone preparation using cyanuric chloride as promoter (Scheme 1). Using sub-stoichiometric quantities of cyanuric chloride in the presence of carboxylic acid **1** and base as a slurry in acetonitrile, diazocarbonyl compounds (**3**) are formed upon addition of ethereal diazomethane.



Scheme 1.

We quickly realized that an evaluation of the reaction conditions employed was necessary. Reaction conditions were optimized in terms of base, solvent, temperature, addition rate and stoichiometry. Although tertiary amines were suitable bases in previous triazine-promoted studies, the formation of a protonated tertiary amine would be problematic when working with either diazo ketones or diazomethane.[2,5,6] Using potassium carbonate ($pK_a = 10.33$)[7] as the base in the synthesis of diazoacetophenone (R = Ph, Scheme 1) improved the yield by 14% compared to the same reaction with diisopropylethylamine (approx. $pK_a = 10.5–11.0$).[8] The selection of potassium carbonate is ideal because it: (1) insures a basic reaction medium; (2) can react with the diazonium ion ($pK_a \approx -2$)[9] derived from diazoketone **3**; and (3) forms innocuous by-products of water and carbon dioxide in the presence of two equivalents of acid.

As was found in the amidation studies, the dipolar aprotic solvent acetonitrile was found to be the best solvent.[4] When issues of insolubility of the carboxylic acid were encountered, THF was used as co-solvent which resulted in no changes in overall yield (vide infra). Using water as co-solvent with either benzoic acid or sodium benzoate, we were able to isolate diazoacetophenone in 35 and 29% yields, respectively. This illustrates a significant advantage with this procedure. These examples provide a unique opportunity in the area of diazo ketone preparation where carboxylic acid derivatives that require the use of either an aqueous medium or are extremely hydrophilic can be used without difficulty.

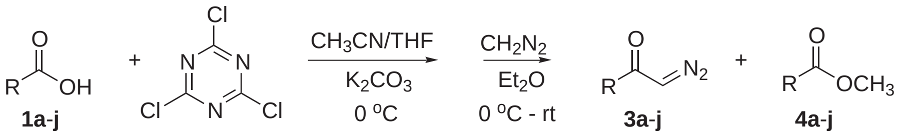
The reaction temperature prior to the addition of ethereal diazomethane also played an important role. Using benzoic acid as the starting carboxylic acid, an optimal reaction temperature of 0°C was observed. Listed below are the results obtained when changing the reaction temperature prior to addition of diazomethane as a function of the percent isolated yield of diazoacetophenone: 23% at 40°C, 48% at 25°C, 58% at 0°C and 18% at −10°C. The mass balances for all the reactions surveyed were excellent (92–97%). In conjunction with diazo ketone formation was isolation of the corresponding methyl ester. Interestingly, no change in the ratio of diazo ketone to methyl ester was observed when performing the reactions under anhydrous conditions. Formation of methyl ester could be attributed to either incomplete addition of the carboxylic acid onto the triazine promoter due to solubility problems or adventitious formation of an anhydride which is known to occur with triazine derivatives.[10] Efforts to provide some insight into the identity of the intermediates responsible for this coupling process via NMR were inconclusive; however, there does exist experimental evidence supporting the formation of peracylated triazine intermediate **2** and not the corresponding acid chloride (Scheme 1).[4,10]

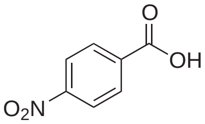
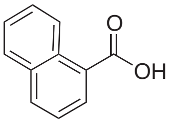
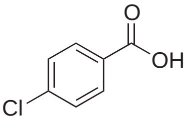
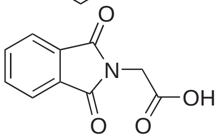
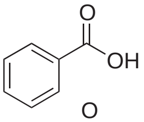
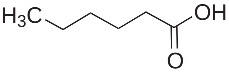
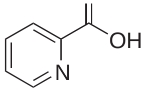
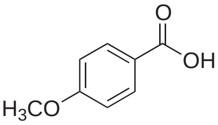
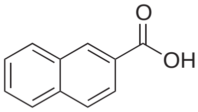
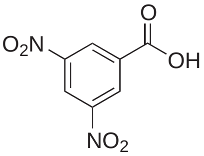
We also observed, using benzoic acid, a moderate change in the isolated yield of diazo ketone when an inverse addition of carboxylic acid and cyanuric chloride was performed, 46% yield (inverse) versus 58% yield (standard). When the rate of addition (mL/min) of the carboxylic acid solution increased, a drop in overall diazo ketone production was observed, 1 min addition (50% yield) versus a 60 min addition (58% yield). Thus a slow addition of the carboxylic acid as a solution in either THF or CH_3CN was found to be superior to other modes of addition. No improvements were observed when the addition was performed over more than 1 h.

The temperature and addition rate studies reveal a delicate balance between both processes of diazo ketone and methyl ester formation. Optimal reaction conditions involved a slow addition of the carboxylic acid as a solution in THF over 1 h to a rapidly stirring slurry consisting of cyanuric chloride and potassium carbonate in CH_3CN at 0°C. The use of a minimum of 2.0 equivalents of potassium carbonate and 2.7 equivalents of diazomethane resulted in higher yields. This insured a basic medium which has been shown to give the best results in diazotization protocols of carboxylic acid derivatives.[6] With optimized conditions in hand, we examined the scope and limitations of this new diazo ketone synthesis (Table 1).[11]

Table 1 reveals some interesting trends. First, aryl carboxylic acids (entries 1–5) were superior to aliphatic carboxylic acids (entry 7). Numerous attempts using a variety of reaction conditions with other aliphatic acids, e.g. hexanoic acid (entry 8), consistently resulted in very low yields of the desired diazo ketone. Aryl derivatives such as picolinic (entry 4) and 2-naphthoic acid (entry 5) afforded the desired diazo ketone in good yield. Second, the efficiency of diazo ketone formation was observed to be sensitive to changes in the electronic properties of the carboxylic acid. Electron deficient (entries 1 and 2) or neutral (entry 3) aryl carboxylic acids were significantly better candidates than their electron rich adducts. 4-Methoxybenzoic acid (entry 9) afforded the desired diazocarbonyl compound in less than 10% yield. Here again, the methyl ester was the main product isolated (82% yield). Interestingly, when 3,5-dinitrobenzoic acid was

Table 1
Triazine-promoted diazo ketone preparation



entry	carboxylic acid	**3**, %[a]	**3**:**4**[b]	entry	carboxylic acid	**3**, %[a]	**3**:**4**[b]
1	**a**, 	50	55:45	6	**f**, 	29	35:65
2	**b**, 	56	61:39	7	**g**, 	29	39:61
3	**c**, 	58	60:40	8	**h**, 	15	18:82
4	**d**, 	66	67:33	9	**i**, 	<10	14:86
5	**e**, 	63	77:23	10	**j**, 	–	2:98

[a] Isolated yields of chromatographically homogeneous spectroscopically pure products are reported. [b] Ratios were determined using NMR analysis of the crude products.

used (entry 10), only a trace of the desired diazo ketone was isolated which indicates that strongly electron deficient carboxylic acids are also not appropriate substrates. The third and final observation involved sterics. Carboxylic acid derivatives without α-methylenes or derivatives which are sterically robust, e.g. 2,2-dimethylpropanoic acid, resulted in no diazo ketone formation.

In summary, a simple protocol has been developed that permits the transformation of aryl carboxylic acid derivatives into diazocarbonyl compounds in good yield using cyanuric chloride as promoter and diazomethane. This procedure can be carried out in water and is affected in one-pot, which is a significant advantage over current methods. Efforts to understand the subtle electronic and steric effects as well as the use of other carbon-based nucleophiles with this technology are underway and will be reported in due course.

Acknowledgements

We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Department of Chemistry and Research Council at the University of South Alabama for support of this research.

References

1. (a) Curtius, T. *Bericht* **1883**, *16*, 2230. (b) Curtius, T. *J. Prakt. Chem.* **1888**, *38*, 396.
2. (a) Regitz, M.; Maas, G. *Diazo Compounds, Properties and Synthesis*; Academic Press: Orlando, 1986. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998.
3. Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.
4. (a) Rayle, H. L.; Fellmeth, L. *Org. Proc. Res. Dev.* **1999**, *3*, 172 and references cited therein. (b) Kaminski, Z. J.; Paneth, P.; Rudzinski, J. *J. Org. Chem.* **1998**, *63*, 4248.
5. Staudinger, H.; Gaule, A. *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 1897.
6. (a) Newmann, M. S.; Beal, P. *J. Am. Chem. Soc.* **1949**, *71*, 1506. (b) Berenbom, M.; Fones, W. S. *J. Am. Chem. Soc.* **1949**, *71*, 1629. (c) Franzen, V. *Justus Liebigs Ann. Chem.* **1957**, *602*, 199. (d) Hauptmann, S.; Hirschberg, K. *J. Prakt. Chem.* **1966**, *34*, 262. (e) Scott, L. T.; Minton, M. A. *J. Org. Chem.* **1977**, *42*, 3757.
7. Perrin, D. D. *Ionization Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed.; Pergamon Press: Oxford, 1982.
8. Brown, H. C.; McDaniel, D. H.; Häflinger, O. *Determination of Organic Structures by Physical Methods*; Braude, E. A., Nachod, F. C., Eds.; Academic Press: New York, 1955; Chapter 14.
9. For diazomethane: McGarrity, J. F.; Smyth, T. *J. Am. Chem. Soc.* **1980**, *102*, 7303. For diazonium derivatives: McGarrity, J. F. *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978; Part 1, Chapter 6. For inorganic acids: Ref. 7. For organic carboxylic acids: Serjeant, E. P.; Dempsey, B. *Ionization Constants of Organic Acids in Aqueous Solution*, 2nd ed.; Pergamon Press: Oxford, 1979.
10. Kaminski, Z. J. *Tetrahedron Lett.* **1985**, *26*, 2901.
11. **Typical procedure for the preparation of diazo ketones 3a–j**: To a 125 mL Erlenmeyer flask containing a large magnetic stir bar was added, in the following order, potassium carbonate (2.0 equiv.), anhydrous CH_3CN (20 mL) and cyanuric chloride (0.4 equiv.). The flask was cooled externally with an ice bath (0°C) and after approximately 5 min a solution of anhydrous THF (20 mL) containing the carboxylic acid (1.0 equiv.) was added via syringe pump over a period of 1 h. The reaction mixture was kept at 0°C for a period of 2 h at which time the contents of the reaction mixture slowly turned into a milky-white slurry. The reaction mixture was allowed to stir for an additional 45 min at which time CH_2N_2 (2.7 equiv.) as a 0°C diethyl ether solution (50 mL) was added in three equal portions. The ice bath containing the reaction mixture was packed with ice and allowed to slowly warm to room temperature as it stirred overnight (approx. 12 h). The crude reaction mixture was transferred to a larger flask (approx. 250 mL) and diluted with diethyl ether (total volume approx. 200 mL). The yellow solution was filtered and concentrated in vacuo. The viscous oil was then immediately purified via silica gel chromatography [hexane/EtOAc, 8/1, 30×60 mm SiO_2, 10 mL fractions] to afford analytically pure diazo ketone.