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Irregularities in the Effect of Potassium Phosphate in Ynamide Synthesis

Karin Dooleweerdt,[†,‡] Henrik Birkedal,[†] Thomas Ruhland,[‡]
and Troels Skrydstrup*,[†]

*Department of Chemistry and the Interdisciplinary
Nanoscience Center, University of Aarhus,
Langelandsgade 140, 8000 Aarhus C, Denmark, and H.
Lundbeck A/S, Department of Medicinal Chemistry and
Support, Ottiliavej 9, 2400 Valby, Denmark*

ts@chem.au.dk

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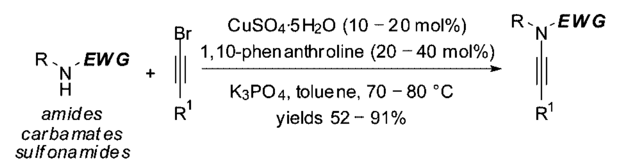
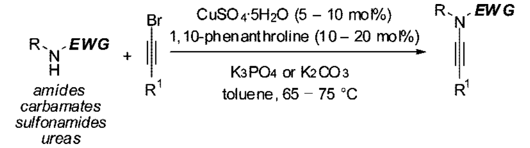


The yields of ynamides using Hsung′s second generation protocol depend substantially on the quality of K_3PO_4. Samples of K_3PO_4 from different suppliers were investigated by various techniques, revealing that the use of pure and anhydrous K_3PO_4 provides higher ynamide yields in comparison to samples contaminated with hydrates ($K_3PO_4 \cdot 1.5H_2O$ and $K_3PO_4 \cdot 7H_2O$). With high quality K_3PO_4, a number of ynamides were synthesized in yields of 52−91%. In addition, we report that ynamides can undergo regioselective hydroamination with carbamates.

Small, reactive building blocks and synthons are paramount in organic synthesis. Recently, ynamides have proven to be versatile and useful reagents in a variety of synthetic organic transformations including various cycloadditions,[1] metathesis,[2] transition metal catalyzed reactions,[3] Pictet−Spengler-type cyclizations,[4] Saucy−Marbet rearrangements,[5] epoxidations,[6] the Kinugasa reaction,[7] DMDO oxidation,[8] in the synthesis of chiral enamides[9] and benzofurans.[10,11]

SCHEME 1. Copper Catalyzed Ynamide Synthesis



In a project directed to using ynamides in cross coupling reactions for the synthesis of heterocyclic systems, we were recently confronted with the task of preparing these functionalized alkynes exploiting Hsung′s second generation protocol (Scheme 1).[12,13] In this procedure, the ynamide is generated by a copper catalyzed coupling between a bromoalkyne and a protected amine such as a carbamate in the presence of either anhydrous K_3PO_4 or K_2CO_3 as the base. Even though this protocol has been optimized through several screenings, lack of reproducibility of yields has been reported from the Tam group.[1e] In our hands, we encountered similar problems in particular when scaling up the reactions to above 1 mmol, which we discovered was linked to the quality of the anhydrous K_3PO_4 obtained from commercial sources. Buchwald and co-workers have reported analogous irregularities of anhydrous K_3PO_4 in Cu-catalyzed amidation reactions.[14] Since K_3PO_4 is frequently used as a base in various transition metal catalyzed reactions, we were therefore encouraged to have a closer look at the quality of this base, from commercial sources, in ynamide synthesis.

[†] University of Aarhus.

[‡] H. Lundbeck A/S.

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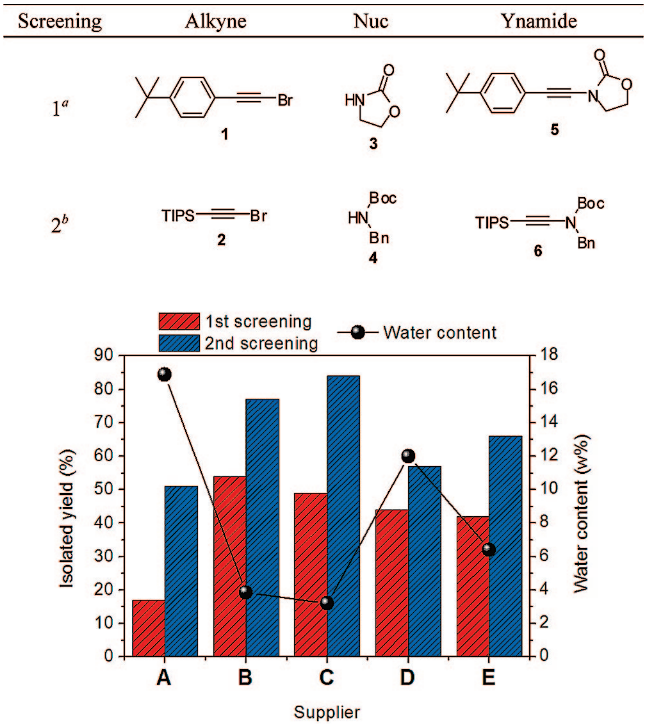

FIGURE 1. Screening of K_3PO_4 from different suppliers and measurement of their water contents.

Five samples (**A**−**E**)[15] of anhydrous K_3PO_4 from different suppliers were investigated by screening them in coupling reactions of two bromoalkynes (**1** and **2**) with carbamates **3** and **4**. The yields of the obtained ynamides **5** (screening 1) and **6** (screening 2) were in the range of 17−54% and 51−84%, respectively. In screening 1, the carbamate **3**, $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline and K_3PO_4 were blanketed with argon, heated to 70 °C in dry toluene (1 M based on **3**) and when the desired temperature was reached, bromoalkyne **1** was added in dry toluene (1 M based on **3**) and the reaction mixture was stirred for 22 h. In screening 2, the Boc-protected amine **4**, $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline and K_3PO_4 were weighed out in an argon-filled glovebox. Dry toluene (0.5 M based on **4**) was added and the reaction mixture was heated to 80 °C. When the desired temperature was reached, a solution of **2** in dry toluene (0.66 M based on **4**) was added and the reaction mixture was stirred for 67 h. The yields of ynamides **5** and **6** in the screening of K_3PO_4-samples from the commercial sources (**A**−**E**) are shown in Figure 1.

As seen from Figure 1, the obtained yields in screening 1 and 2 depend significantly on the commercial source of K_3PO_4. K_3PO_4-samples **B** and **C** performed best followed by sample **D** and **E**, while sample **A** was considerably less efficient. To elucidate the reason to these significant variations, a selection of characterization studies were performed on the K_3PO_4-samples.

Analysis of the K_3PO_4-samples by powder X-ray diffraction (PXRD) showed that they were mixtures of anhydrous K_3PO_4 and hydrates to different extents. In particular, sample **A**, displaying the poorest performance, is composed mainly of a mixture of $K_3PO_4 \cdot 1.5H_2O$, $K_3PO_4 \cdot 7H_2O$ and only a very minor fraction of anhydrous K_3PO_4 if any at all.[16] On the other hand, samples **B** and **C** consist of almost pure anhydrous K_3PO_4 with minor impurities of $K_3PO_4 \cdot 7H_2O$ and $K_3PO_4 \cdot 1.5H_2O$, which correlates well with their performance in screening 1 and 2. Samples **D** and **E** are mainly anhydrous K_3PO_4, but with clear indications of hydrate impurities. These results suggest an important correlation of the composition of the employed K_3PO_4 and the yield obtained in ynamide synthesis.

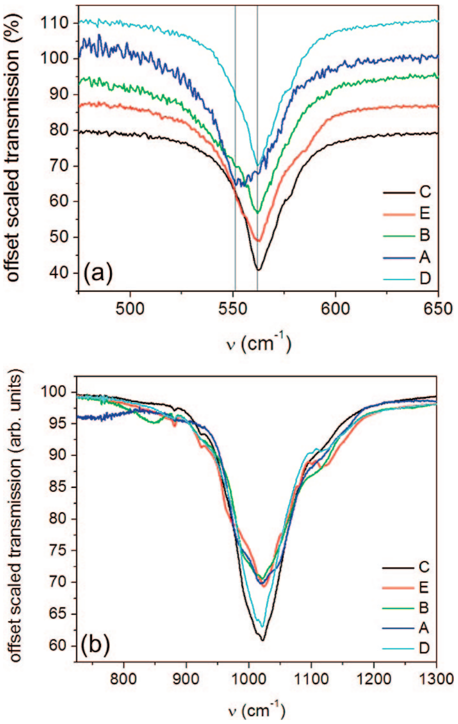

FIGURE 2. (a) Rescaled and offset FTIR data in the 475−650 cm^{-1} region. The vertical lines indicate the maximum peak positions for the phosphate adsorption in the **C** and **A** samples, respectively. (b) Rescaled and offset FTIR data in the 725−1300 cm^{-1} region.

Infrared spectroscopy supports the above findings (Figure 2). The phosphate signature vibrations around 560 and 1000 cm^{-1} were fitted to allow quantitative comparison of the IR signals.[17] Samples **B**−**D** display a main absorption at 562 cm^{-1} (see Figure 2a), whereas the main adsorption for sample **A** is lower. PXRD data showed that sample **A** contained essentially no anhydrous K_3PO_4. Hence, the lack of a main absorption at approximately 562 cm^{-1} can be taken as an indicator of poor material. Around 900−1000 cm^{-1}, the phosphate group has a series of strong IR-bands (see Figure 2b). This region was also fitted. In all samples there is a minor, sharp absorption at 922 cm^{-1}, except for sample **A**. The presence of a sharp, albeit weak, absorption at 922 cm^{-1} can be taken as a signature of anhydrous K_3PO_4. The main IR absorptions occur in a cluster of peaks around 1030 cm^{-1}. The overlaps between the hydrates and anhydrous K_3PO_4 mean that simple inspection of the obtained IR spectra alone is not sufficient for confident determination of sample purity; instead we recommend the use of powder X-ray diffraction.

To substantiate and quantify the above findings, the samples were subjected to thermagravimetrical analysis (TGA). The

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(15) K_3PO_4 was obtained from the following sources: (**A**) from Sigma Aldrich (P5629), (**B**) from Riedel-de Haën through Sigma Aldrich/Fluka (04347), (**C**) from Acros Organics (38768), (**D**) from Strem Chemicals (19−3800), and (**E**) from Alfa Aesar (041587).

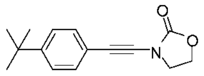
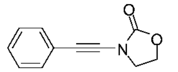
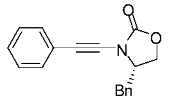
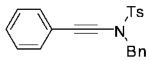
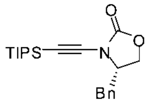
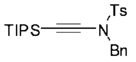
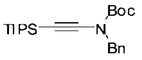
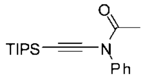
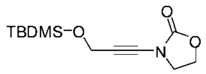
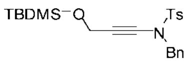
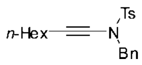
(16) For further information on the powder X-ray diffraction analysis, see the Supporting Information.

(17) Fits were done to a sum of Lorentzians including a background term and possibly an auxiliary peak for leveling background to left/right of peak cluster and/or describing details of neighboring peaks. See Supporting Information for further details on the analysis by infrared spectroscopy.

samples were heated to 350 °C, while the mass of the sample was measured simultaneously to visualize the water content in the samples. The curve plotted against the right-hand *y*-axis in Figure 1 illustrates the mass loss as measured by TGA.[18] The deviations among the K_3PO_4 samples **A**−**E** are significant and varying in the range of 3−16%. The measured mass loss correlates well with the performance of the K_3PO_4 samples in the ynamide synthesis. Again sample **A** stands alone with a mass loss of 16 wt%, followed by sample **D** (12 wt%) and **E** (6 wt%). Sample **B** and **C** perform best with mass losses of only 3−4 wt%. In short, K_3PO_4-samples **B** and **C** provide the highest yields in our screenings. When investigated more closely they appear to consist to a high degree of pure anhydrous K_3PO_4.[19,20]

With these results in hand, a variety of ynamides were synthesized using the commercial source of K_3PO_4 (samples **B** or **C**) with highest purity (Table 1). The yields for the coupling between aryl bromoalkynes and 2-oxazolidinones were obtained in the range of 52−72% (entries 1−3), where the major byproducts of this reaction arose from competing Glaser-type homocoupling.[21] Ynamide **5** could be isolated in a similar yield when K_2CO_3 was employed in place of K_3PO_4. Earlier we have been unable to obtain ynamide **7** in a satisfactory yields. When the reaction scale was increased from 1−2 mmol to 5−10, the yields dropped to 40%. After changing the source of K_3PO_4 **A** to **B** we have been able to obtain a 72% yield on a 50 mmol scale. Ynamide **8** was isolated in a 66% yield equivalent to the 60−71% obtained by Hsung et al. in the coupling of (bromo-ethynyl)benzene with (R)-4-benzyloxazolidin-2-one.[12a] With the more acidic sulfonamide, a high yield of 88% (10 mmol scale, improved from 73%) was secured (entry 4). In the case of the TIPS-substituted bromoalkynes (entries 4−8), no Glaser products were observed and the yields were therefore generally higher, attaining 91% (entries 5 and 6). In this case ynamide **10** was obtained in 91% yield on a 56 mmol scale; this result correlates well with the yield of 89% obtained by Hsung and co-workers in the coupling of (bromo-ethynyl)-triisopropylsilane with (*R*)-4-benzyloxazolidin-2-one on a 48 mmol scale.[12a,b] Earlier we have only been able to isolate **10** in 40% yield. In the case of **11** we have succeeded in increasing the yield from 51% to a very good yield (91%). Satisfactory yields were also furnished in representative couplings of the bromoalkyne of TBDMS-protected propargylic alcohol with an oxazolidinone and a sulfonamide (entries 9 and 10). When coupling a sulfonamide to a non functionalized alkyne, such as 1-bromo-hex-1-yne (entry 11) the ynamide product was obtained in a 64% yield.

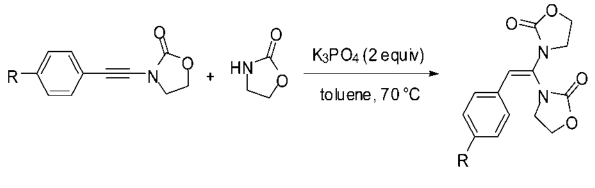
TABLE 1. Synthesized Ynamides

entry	product[a]		time	K_3PO_4 source	yield[b]
1		**5**	22 h	B	54%
2		**7**	23 h	B	72%
3		**8**	23 h	B	66%
4[d]		**9**	22 h	B	88%
5		**10**	43 h	B	91%
6		**11**	38 h	B	91%
7[c]		**6**	67 h	C	84%
8		**12**	44 h	B	66%
9		**13**	46 h	B	52%
10[d]		**14**	22 h	B	86%
11		**15**	20 h	B	64%

[a] Reaction conditions: Argon atmosphere, nucleophile (1 equiv), bromoalkyne (1.1 equiv), $CuSO_4 \cdot 5H_2O$ (10 mol%), 1,10-phenanthroline (20 mol%), K_3PO_4 (2 equiv), toluene (0.5 M based on nucleophile), 70 °C. [b] All yields are isolated yields after column chromatography on silica gel. [c] Reaction conditions: Argon atmosphere, nucleophile (1.2 equiv), bromoalkyne (1 equiv), $CuSO_4 \cdot 5H_2O$ (20 mol%), 1,10-phenanthroline (40 mol%), K_3PO_4 (2.4 equiv, toluene (0.33 M based on nucleophile), 80 °C. [d] Reaction conditions: Argon atmosphere, nucleophile (1 equiv), bromoalkyne (1.5 equiv), $CuSO_4 \cdot 5H_2O$ (10 mol%), 1,10-phenanthroline (20 mol%), K_3PO_4 (2 equiv), toluene (0.5 M based on nucleophile), 70 °C.

Finally, we briefly report an unexpected regioselective hydroamination as side reaction that was discovered during our investigations. In the coupling reaction between **1** and **3**, we isolated small amounts of the ketenaminal **16** (Scheme 2). To examine whether this product was arising from the addition of carbamate to the ynamide, we therefore treated both ynamides **5** and **7** with 1.1 equivalents of 2-oxazolidinone (**3**) and a 2-fold excess of K_3PO_4 (Scheme 2). The reactions gave exclusively one regioisomer in both cases providing the hydroamination products **16** and **17** in 59 and 68% yield, respectively. Further work is underway to investigate the scope of this reaction.

SCHEME 2. Base-Mediated Hydroamination of Ynamide



16 (R = *t*Bu): 59%
17 (R = H): 68%

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(18) For further information on the results achieved by T.G.A., see the Supporting Information.

(19) The use of $CuSO_4 \cdot 5H_2O$ as the catalyst for ynamide synthesis provides contamination of the reaction mixture with water. However, with the loadings of K_3PO_4 used for each reaction, at least 1.7 equiv. of anhydrous K_3PO_4 would be present.

(20) In the case of K_3PO_4 received as "chunks" and not a powder, the yields can be increased to some extent by grinding of the material. But it is not sufficient to convert it into a more effective K_3PO_4. Drying has been attempted at 150 °C for several hours with no success.

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In summary, we have identified a possible reason for the irregularities in the Hsung protocol seen by us and others, when using K_3PO_4 as the base. The yields of the ynamide synthesis appear to depend highly on the purity of the base. The qualities of K_3PO_4 from five different commercial sources were examined by powder X-ray diffraction, thermagravimetrical analysis and IR-spectroscopy. Highest yields of ynamides are obtained in the case of pure and anhydrous K_3PO_4. In addition, we have found that ynamides in certain cases can be converted into ketenaminals with carbamates by a regioselective hydroamination reaction.

Experimental Section

General Procedure for the Cu-Catalyzed Coupling of an Amide or Carbamate with a Bromoalkyne. Ynamides are synthesized according to literature procedure.[12b] Carbamate or amide (1 equiv), $CuSO_4 \cdot 5H_2O$ (0.10 equiv), 1,10-phenanthroline (0.20 equiv), and K_3PO_4[22] (2 equiv) were heated to 70 °C in dry toluene (1 M based on carbamate) under an atmosphere of argon, then bromoalkyne (1.1−1.5 equiv) was added in dry toluene (1 M based on carbamate) followed by stirring until the carbamate was consumed or the reaction has stopped as determined by thin layer chromatography. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc, filtered through a thin pad of Celite and then concentrated *in vacuo*. The obtained crude material was purified by flash chromatography on silica gel.

Procedure for the Cu-Catalyzed Coupling of tert-Butylbenzyloxycarbamate with (Bromoethynyl)triisopro-pylsilane. Ynamide **6** was synthesized according to literature procedure.[3a] **4** (2.40 mmol, 497 g), $CuSO_4 \cdot 5H_2O$ (2.40 mmol, 497 g), 1,10-phenanthroline (0.80 mmol, 144 mg), and K_3PO_4[23] (4.80 mmol, 1.02 g) were mixed in an argon-filled glovebox and then heated to 80 °C in dry toluene (0.66 M based on **2**, then **2** (2.0 mmol, 523 mg) was added in dry toluene (0.66 M) followed by stirring for 67 h. The reaction mixture was cooled to room temperature, diluted by EtOAc, filtered through a pad of Celite and concentrated *in vacuo*. After column chromatography (Et_2O in pentane in a gradient from 0−2%) the title compound was obtained as a brown oil (654 mg, 1.69 mmol, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38−7.28 (m, 5H), 4.57 (s, 2H), 1.49 (s, 9H), 1.02 (s, 3H), 1.01 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.3, 136.5, 128.7, 128.6 (2C), 127.9 (2C), 98.0, 82.6, 68.6, 53.2, 28.3 (3C), 18.8 (6C), 11.5 (3C). HRMS (ES) calcd for $C_{23}H_{37}NO_2SiNa$ (MNa^+) 410.2486, found 410.2482.

3,3′-(2-(4-tert-Butylphenyl)ethene-1,1-diyl)dioxazolidin-2-one (15). **7** (243 mg, 1.00 mmol), 2-oxazolidinone (96 mg, 1.1 mmol), K_3PO_4[22] (651 mg, 2.00 mmol), and dry toluene (0.5 M based on **16**) were mixed and then heated to 70 °C and stirred for 24 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc, filtered through a thin pad of Celite and concentrated *in vacuo*. After column chromatography (1:1 EtOAc in pentane) the title compound was obtained as a colorless solid (194 mg, 0.587 mmol, 59%). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38 (dt, 2H, J = 8.4 Hz, 2.0 Hz), 7.28 (dt, 2H, J = 8.4 Hz, 2.4 Hz), 6.11 (s, 1H), 4.47 (dd, 2H, J = 9.2 Hz, 7.6 Hz), 4.43 (dd, 2H, J = 8.4 Hz, 6.8 Hz), 4.08 (dd, 2H, J = 9.2 Hz, 7.6 Hz), 3.74 (dd, 2H, J = 9.6 Hz, 8.4 Hz), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.8, 155.3, 151.5, 130.2, 129.2, 127.9 (2C), 125.9 (2C), 117.8, 63.5, 62.6, 47.8, 45.1, 34.8, 31.4 (3C). HRMS (ES) calcd for $C_{18}H_{22}N_2O_4Na$ (MNa^+) 353.1477, found 353.1473. mp = 161−163 °C.

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Supporting Information Available: Experimental details of all new and known ynamides and spectroscopic data of all ynamides and unknown compounds, powder X-ray diffraction, thermal gravimetrical and infrared spectroscopy data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] K_3PO_4 obtained from Riedel de-Haën (**B**).

[23] K_3PO_4 obtained Acros Organics (**C**).