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Phosphorus(III)-Mediated Reductive Condensation of α-Keto Esters and Protic Pronucleophiles

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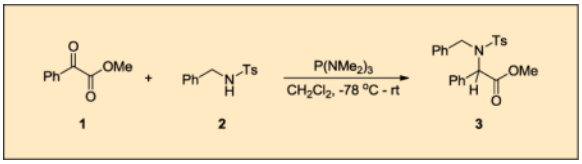
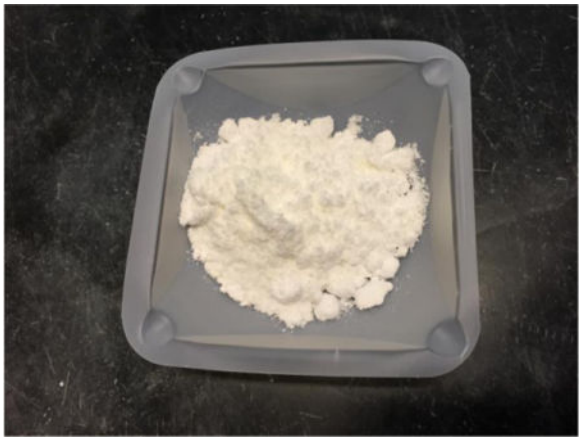
Graphical abstract



Procedure

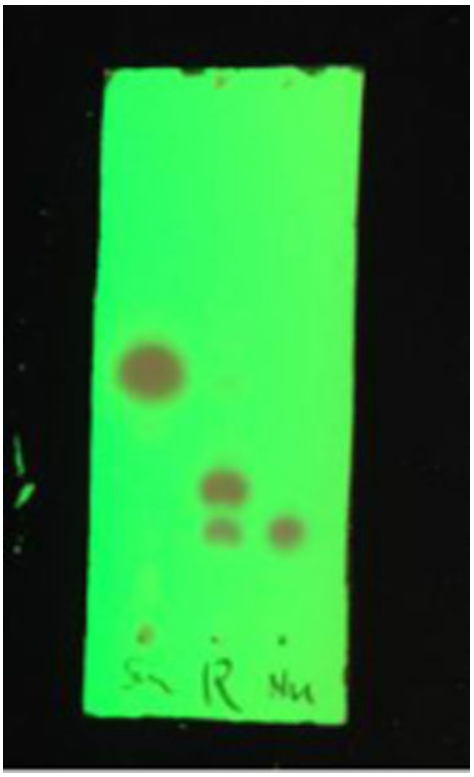
A. *Methyl 2-(N-Benzyl-4-Methylphenylsulfonamido)-2-Phenylacetate (**3**)*. 4-Methyl-*N*-(phenylmethyl)benzenesulfonamide (**2**) (8.49 g, 32.5 mmol, 1.1 equiv) was placed in an oven-dried 1-L 2-neck round bottom flask equipped with a magnetic stir bar (3/8 × 1 ½", Teflon-coated, octagon). The center neck of the reaction flask was fitted with a rubber septum-capped 60-mL pressure-equalizing addition funnel, and the side neck was fitted with a rubber septum with nitrogen inlet (as shown in the image below). The reaction vessel was then purged with nitrogen atmosphere by three evacuation-backfill cycles (Notes 1). Dry dichloromethane (296 mL, 0.1 M) was added to the round bottom flask via cannula transfer from an oven-dried 1-L Schlenk Flask (Notes 2). Methyl benzoylformate (**1**) (4.20 mL, 4.85 g, 29.6 mmol, 1.0 equiv) was added to the solution through the side neck (Notes 3). The addition funnel was then charged with tris(dimethylamino)phosphine (5.90 mL, 5.30 g, 32.5 mmol, 1.1 equiv) through the septum on top (Notes 4). Dichloromethane (33 mL) was added to the addition funnel in the same way using a 60-mL syringe and an oven-dried steel needle. The reaction flask was cooled to –78 °C with a dry ice-acetone bath in a 3-L Dewar flask (Notes 5). The tris(dimethylamino)phosphine solution was added dropwise to the flask over 20-30 min while stirring (Notes 6 and 7). Upon complete addition of the tris(dimethylamino)phosphine solution, the cooling bath was removed and the reaction mixture was stirred for 2 h, during which time it warmed to ambient temperature (Notes 8).

When the reaction reached completion as determined by TLC (Notes 9), the dropping funnel was removed and distilled water (300 mL) was added to the reaction mixture in one portion. The biphasic mixture was then transferred to a 1-L separatory funnel. The organic layer was separated, washed with saturated aqueous sodium chloride solution (3 × 400 mL), dried over anhydrous sodium sulfate (150 g) for 15 minutes (Notes 10). The sodium sulfate was filtered and the solution was concentrated in vacuo using a rotary evaporator (ca. 100 mmHg, water bath temperature 30 ˚C). The crude residue was purified by silica gel flash column chromatography using EtOAc and hexanes as eluent (Notes 11, 12, 13 and 14), yielding the title compound as an air and moisture stable white solid (9.44 – 10.09 g, 78 – 83 %, picture shown below).



Notes

1. 4-Methyl-*N*-(phenylmethyl)benzenesulfonamide was synthesized according to the known procedure: Coste, A.; Couty, F.; Evano, G. *Org. Synth.* **2010**, *87*, 231.
2. Dichloromethane was purchased from Fischer Scientific (Product Number: D138-4) and degassed by bubbling argon for 1.5 h before passed through an activated alumina column using a Glass Contour solvent system. The solvent is collected using an oven-dried 1-L Schlenk flask as receiving flask, which was purged with argon atmosphere by three evacuation-backfill cycles.
3. Methyl benzoylformate (>97.0%) was purchased from TCI (Product Number: B1033) and used as received.
4. Tris(dimethylamino)phosphine (97%) was purchased from Alfa Aesar (Product Number: A12571) and used as received.
5. 4-Methyl-*N*-(phenylmethyl)benzenesulfonamide may not be completely dissolved at this temperature.
6. The rate of the addition was held at approximately 2 drops per second.
7. The mixture was stirred at 600 rpm throughout the reaction.
8. The reaction should remain colorless to faint yellow. A bright yellow color usually indicates the formation of side products.
9. Thin layer chromatograph was performed on silica gel 60 F_{254}TLC plate (EMD Millipore TLC Silica Gel 60 Glass Plates, purchased from Fischer Scientific, Product Number: M1057150001) with 1:6 EtOAc:Hexanes as eluent. The following R_f values were observed (visualized under 254 nm UV light): R_f (methyl benzoylformate): 0.40; R_f (4-methyl-*N*-(phenylmethyl)benzenesulfonamide): 0.14; R_f (product): 0.22. Picture of TLC plate is shown below (lane “SM”: methyl benzoylformate; lane “R”: reaction mixture; lane “Nu”: 4-methyl-*N*-(phenylmethyl)benzenesulfonamide):



10. Sodium chloride and sodium sulfate were purchased from VWR and used as received.

11. Silica gel (230-400 mesh) was purchased from SiliCycle (Product Number: R12030B) and used as received.

12. Ethyl acetate and hexanes were purchased from Fischer Scientific and used as recived.

13. Dichloromethane (5 mL) was added to the crude mixture. The crude product was loaded onto a column packed with silica gel slurry in 1:10 EtOAc:Hexanes (column is 9 cm in diameter, height of silica gel was 25 cm). After 1 L of initial elution, 1:8 EtOAc:Hexanes was used as eluent and 150 mL fractions were collected.

14. The product has the following spectral characteristics: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.3, Hz, 2H), 7.19-7.16 (m, 3H), 7.15-7.10 (m, 2H), 7.02 (dd, J = 5.0 Hz, J = 1.6 Hz, 3H), 6.87-6.85 (m, 2H), 5.79 (s, 1H), 4.64 (d, J = 16.3 Hz, 1H), 4.41 (d, J = 16.3 Hz, 1H), 3.57 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 143.5, 137.5, 137.0, 133.5, 129.5, 129.4, 128.9, 128.7, 128.0, 127.8, 127.5, 126.8, 63.2, 52.2, 49.4, 21.6; IR (neat): 2950, 2500, 2160, 2024, 1741, 1598, 1493, 1449, 1335, 1290, 1200, 1141, 1092, 1046, 979, 927, 862, 815, 744, 692, 661 cm^{-1}; mp 96-98 °C; HRMS (EI): m/z calcd for $C_{23}H_{24}NO_4S$ [M+H] 410.1426, found 410.1429; Anal. Calcd for $C_{23}H_{23}NO_4S$: C 67.46, H 5.66, N 3.42, O 15.63 S 7.83, found: C 67.64, H 5.97, N3.48, O 15.60, S 7.88.

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Discussion

Phosphorus(III) reagents are known to undergo reaction with 1,2-dicarbonyl compounds to give adducts of formal *P*-addition to the carbonyl oxygen (Kukhtin-Ramirez reaction).[2] We have shown that these Kukhtin-Ramirez adducts further react to incorporate a range of *N*-, *O*-, and *C*-based protic pronucleophiles with expulsion of a phosphine oxide by-product.[3,4] The process likely proceeds in stepwise fashion, initiated by proton transfer from the protic pronucleophile to the Kukhtin-Ramirez adduct, followed by Arbuzov-like displacement of the phosphine oxide leaving group. This reaction sequence therefore represents a convenient one pot process for access to a range of α–functionalized carbonyl compounds from readily available reagents and precursors.[3,4]

The synthetic method is exemplified in the above procedure, which demonstrates the synthesis of methyl 2-(*N*-benzyl-4-methylphenylsulfonamido)-2-phenylacetate (**3**), an α–amino ester derivative.[5] By direct reductive construction of the α-C-N bond, our approach takes advantage of the wide available α–keto esters as starting materials, and provides an operationally simple and chemoselective alternative to transamination and reductive amination strategies.[6,7] Furthermore, since this method does not involve the intermediacy of imine equivalents, useful C-N bonds from N-pronucleophiles that do not form imines (e.g. azoles) can be successfully synthesized using this method (Table 1).[7]

The reaction is tolerant of a range of solvents (CH_2Cl_2, THF, PhMe), but the use of dichloromethane reliably provides the highest yields and streamlines the aqueous workup on the laboratory scale. The use of commercially available $P(NMe_2)_3$ results in the formation of $O=P(NMe_2)_3$ (i.e. HMPA), a water soluble byproduct that is readily eliminated by aqueous extraction. In view of potential handling concerns resulting from the toxicity of HMPA, we note that the use of alternative phosphorous triamide reagents, specifically tris(1-pyrrolidinyl)phosphine (which generates a less toxic phosphorus(V) oxide by-product), provide similarly satisfactory results (Scheme 1, 1.8 mmol scale).[8]

As noted in our previous studies, the scope of the reaction with respect to protic pronucleophile includes diverse *O*-based (phenols, carboxylic acids and some alcohols) and *C*-based (readily enolizable 1,3-dicarbonyls and related derivatives). The selection of protic pronucleophile is bracketed by pK_a, with only those species capable of proton transfer to the Kukhtin-Ramirez adduct (pK_a ca. 25-27 in DMSO) being reactive under these conditions (Table 2).

Appendix Chemical Abstracts Nomenclature (Registry Number)

4-Methyl-*N*-(phenylmethyl)benzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-(phenylmethyl)-; (1576-37-0)

Dichloromethane: Methane, dichloro-; (75-09-2)

Methyl benzoylformate: Benzeneacetic acid, α-oxo, methyl ester; (15206-55-0)

Tris(dimethylamino)phosphine: Phosphorus triamide, *N,N,N,N′,N′,N′*-hexamethyl-; (1608-26-0)

Sodium Chloride: sodium chloride; (7647-14-5)

Sodium Sulfate: sulfuric acid sodium salt (1:2); (7757-82-6)

Biographies

Wei Zhao is from Jinan, Shandong Province, P. R. China. He completed his BSc at Xiamen University, working with Prof. Pei-Qiang Huang and Prof. Xiao Zheng. In fall 2010 he joined Penn State Chemistry working with Prof. Alexander Radosevich. He is now a senior graduate student with research focused on redox catalysis at geometrically constrained organophosphorus compounds.

Alex Radosevich is from Waukegan, IL and received his B.S. from Notre Dame (2002). He obtained a Ph.D. from UC Berkeley (2007) working with Prof. Dean Toste. Following postdoctoral research at MIT with Prof. Dan Nocera, he joined the department of chemistry at Penn State in 2010 as an assistant professor, where his research has focused on the design, development, and implementation of new synthetic methodology.

References

1. Department of Chemistry, Pennsylvania State University, University Park, PA 16802, radosevich@psu.edu. We thank NIGMS (GM114547), Alfred P. Sloan Foundation, and the Pennsylvania State University for funding.0
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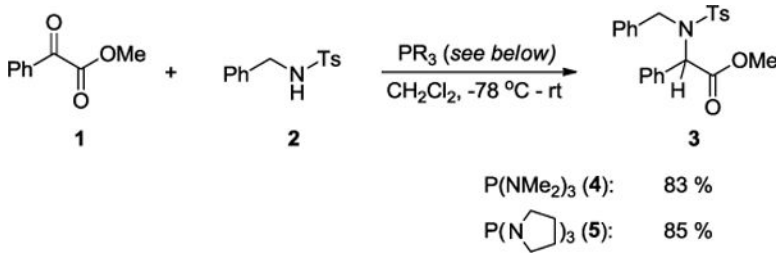
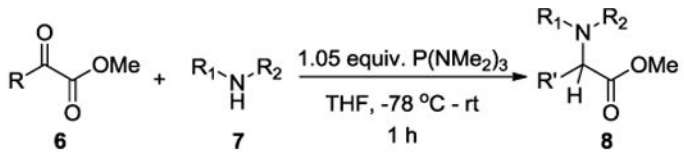


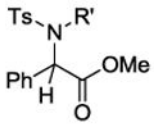
Scheme 1

Phosphorus(III)-mediated synthesis of α-amino esters.

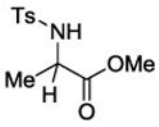
Table 1

Scope of the phosphorus(III)-mediated α-amino ester synthesis.[a]

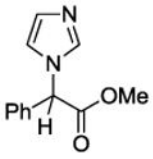




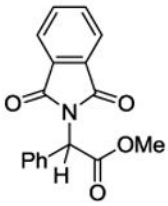
8aa, R' = H, 70%
8ab, R' = Ph, 89%
8ac, R' = Bn, 82%
8ad, R' = allyl, 85%
8ae, R' = $(CH_2)_2OTBS$, 85%



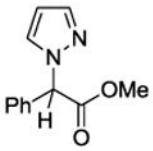
8b, 60 %



8c, 60 %



8d, 83 %



8f, 83 %

[a]Yield under literature reported conditions.[2]

Table 2

Additional examples of Phosphorus(III)-mediated carbonyl functionalization with *O*- and *C*- pronucleophiles.