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Short Note

[(*N*-benzamidomethyl)(*N*-benzoyl)amino] methyltriphenylphosphonium Tetrafluoroborate

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Abstract: In this study, [(*N*-benzamidomethyl)(*N*-benzoyl)amino]methyltriphenylphosphonium tetrafluoroborate was synthesized at 80 °C, starting from *N*-benzoylaminomethyltriphenylphosphonium tetrafluoroborate, by a specific α-amidoalkylation reaction using Hünig's base as a catalyst. *N*-benzoylaminomethyltriphenylphosphonium tetrafluoroborate acts as both an amidoalkylating agent and a nucleophile precursor. The structure of the compound obtained was confirmed by spectroscopic methods (^{1}H-, ^{13}C-, ^{31}P-NMR, IR) and HR-MS analysis.

Keywords: triphenylphosphonium salts; amide; building blocks; α-amidoalkylation; α-amidoalkylating agents

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1. Introduction

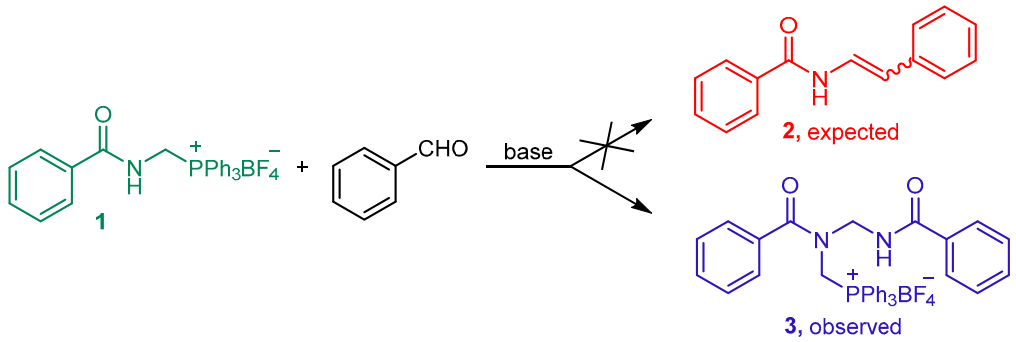
α-amidoalkylating agents are a group of compounds with a diverse structure that can be used as convenient building blocks in organic synthesis to the C–C and C–heteroatom bond formation. We can distinguish here such compounds as α-amido sulfones, *N*-(1-benzotriazolyl)alkylamides, *N*-(1-alkoxyalkyl)amides, or *N*-(1-hydroxyalkyl)amides [1–17]. In addition, 1-aminoalkylphosphonium derivatives may also be included in this synthetically useful group of organic compounds. Their specific structure, primarily the presence of a phosphonium group in the immediate vicinity of the amino group, gives them unique properties. As equivalents of *N*-acyliminium cations, they show high reactivity in α-amidoalkylation reactions [8,18,19]. On the other hand, due to the presence of a phosphonium group, they can be considered as potential precursors of ylides in Wittig reactions. However, this application encounters certain limitations, the most important of which is that they are more susceptible to elimination than to ylide formation [18,20,21].

This work presents one of the examples confirming the unusual reactivity of *N*-acylaminomethylphosphonium salts leading to the formation of amidoalkylation products under conditions rather typical for the Wittig reaction.

2. Results and Discussion

Based on research on the ylides generation from structurally similar methyl *N*-acyl-α-triphenylphosphonioglycinate tetrafluoroborates described by Kuźnik in 2004 [21], we selected the conditions under which we carried out the reaction of *N*-benzoylaminomethyltriphenylphosphonium tetrafluoroborate **1** and benzaldehyde, hoping to obtain the Wittig reaction product **2** (see Scheme 1). Unfortunately, none of the applied protocols worked (entries 1–8), and only in some cases trace amounts of the expected product **2** were obtained (entries 1, 2, and 6). Changing the solvent or base had no positive effect on the course of the Wittig reaction. However, to our surprise, in the case of Et_3N and DIPEA (*N*,*N*-diisopropylethylamine, Hünig's base) we detected the presence of an unexpected compound in the reaction mixtures. After optimization of the reaction conditions (time,

solvent, temperature), we isolated the obtained product and elucidated its structure (^{1}H-, ^{13}C-, ^{31}P-NMR, MS—see also Supplementary Materials). The synthesis proceeds smoothly at room or elevated temperature (7 days or 80 °C, 10 h, respectively) in CH_3CN in the presence of DIPEA (entries 7–8). Lower yields were obtained by conducting the transformation in THF in the presence of Et_3N (entries 1–2). Moreover, it turned out that benzaldehyde was not involved in the reaction at all (compare entries 7–9), which enabled a quick analysis of the results and elucidation of the structure of product **3**.



Entry	Base	Molar Ratio 1:Aldehyde:Base	Temp., °C	Solvent	Time, h	Yields, % [a]	
						2	3
1	Et_3N	1:4:1.25	rt	THF	24/168	traces	8/16
2	Et_3N	1:4:1.25	80	THF	4/10	traces	43/46
3	LDA [b]	1:4:1.25	rt	THF	24	-	-
4	*t*-BuOK	1:4:1.25	rt	THF	4	-	-
5	DIPEA [c]	1:4:1.25	rt	THF	48	-	5
6	DIPEA	1:4:1.25	80	THF	3	traces	48
7	DIPEA	1:4:1.25	rt	CH_3CN	2/72/168	-	2/60/**73** [d]
8	DIPEA	1:4:1.25	80	CH_3CN	4/10	-	63/67
9	DIPEA	1:-:1.25	80	CH_3CN	10	-	**62** [d]

[a] Estimated yields (the reaction progress was monitored by ^{1}H-NMR); [b] lithium diisopropylamide: LDA/THF (2M solution); [c] *N*,*N*-diisopropylethylamine; [d] isolated yields.

Scheme 1. Reaction of *N*-benzoylaminomethyltriphenylphosphonium tetrafluoroborate **1** and benzaldehyde in the presence of base—conditions and results.

The progress of the transformation can be monitored by ^{1}H- and ^{31}P-NMR spectroscopy (Figure 1). In the ^{31}P-NMR spectrum, during the conversion of *N*-benzoylaminomethyltriphenylphosphonium tetrafluoroborate **1**, the disappearance of the singlet at 21.0 ppm and the appearance of the singlet at 19.4 ppm was observed. At the same time, the doublet of doublets (5.32 ppm, J = 6.1, 3.1 Hz) disappears in the ^{1}H-NMR spectrum and two doublets (5.42 ppm, J = 4.6 Hz; 5.10 ppm, J = 6.8 Hz) appear. The analysis of the integrals indicates that there is one NH group in the product: 8.31 (t, J = 6.0 Hz, 1H). The proposed structure **3** was confirmed by HR-MS.

Considering the obtained results, the explanation for the formation of compound **3** may be that in the presence of an appropriate base, the phosphonium salt **1** becomes both a precursor of the nucleophile and the amidoalkylating agent. To the best of our knowledge, this type of reaction has not yet been described in the literature.

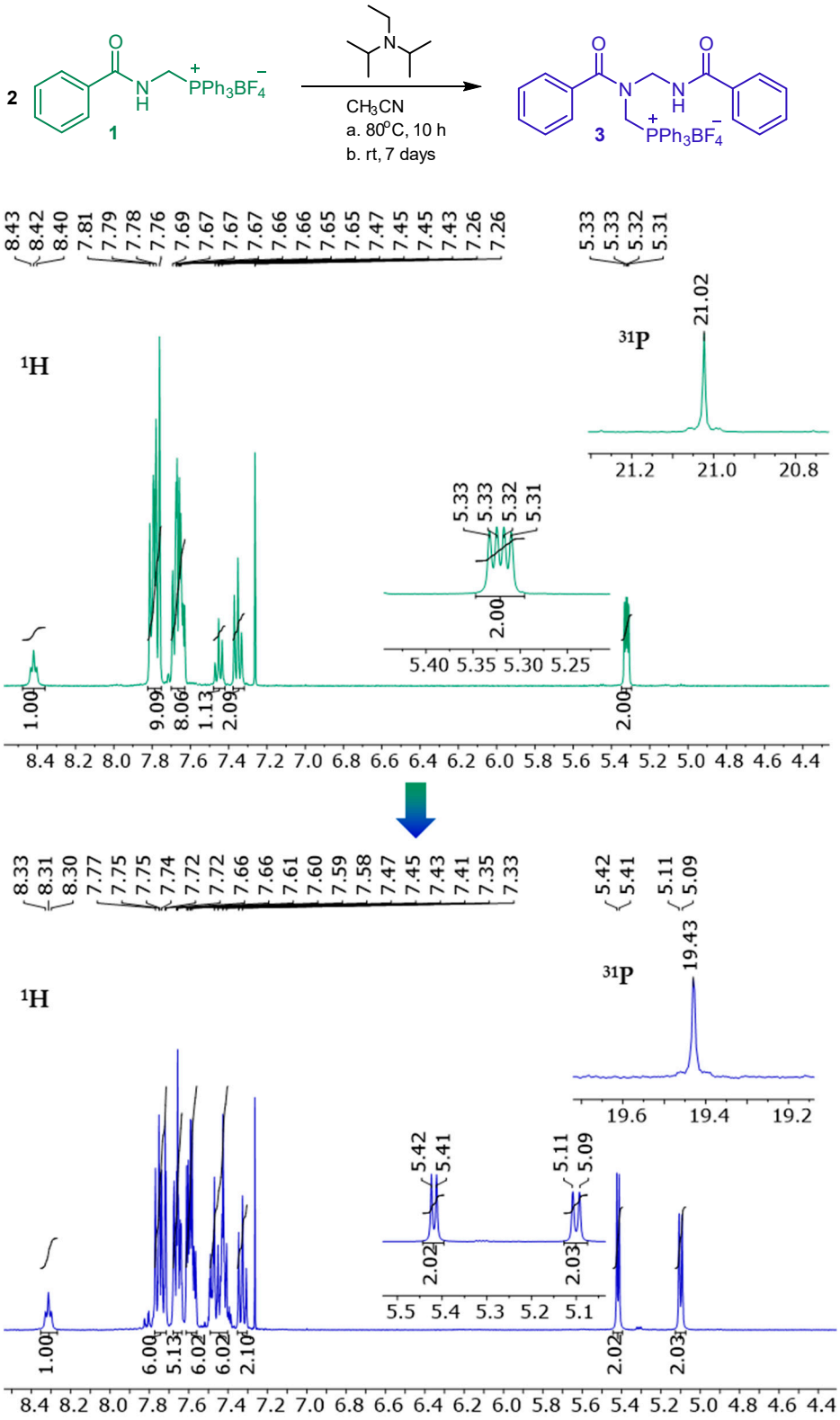


Figure 1. Transformation of *N*-benzoylaminomethyltriphenylphosphonium tetrafluoroborate **1** into [(*N*-benzamidomethyl)(*N*-benzoyl)amino]methyltriphenylphosphonium tetrafluoroborate **3**, with changes in the characteristics of the ^{1}H- and ^{31}P-NMR spectra.

3. Materials and Methods

3.1. General

All commercially available reagents and solvents were used without further purification. *N*-benzoylaminomethyltriphenylphosphonium tetrafluoroborate **1** was prepared according to our previously described procedure [22]. The melting point was determined in a glass capillary and was uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at operating frequencies of 400 and 100 MHz, respectively, using tetramethylsilane (TMS) as the resonance shift standard. ^{31}P-NMR spectra were recorded at an operating frequency of 161.9 MHz without the resonance shift standard, and with respect to H_3PO_4 set as 0 ppm. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. The IR spectrum was recorded using an FT-IR spectrometer (ATR method). High-resolution mass spectrometry (HR-MS) analyses were performed on a Waters Xevo G2 Q-TOF mass spectrometer equipped with an ESI source operating in positive ion mode.

3.2. [(N-benzamidomethyl)(N-benzoyl)amino]methyltriphenylphosphonium Tetrafluoroborate **3**

N-benzoylaminomethyltriphenylphosphonium tetrafluoroborate **1** (0.25 mmol, 121 mg), benzaldehyde (1.0 mmol, 106.1 mg, 102.0 μL), and acetonitrile (1 mL) were placed into a flame-dried glass vial (5 mL). After a few minutes of mixing, Hünig's base (0.313 mmol, 40.4 mg, 54.4 μL) was added. The vial was purged with argon and sealed with a screw-cup. The reaction was carried out at 80 °C for 10 h. The main product **3** was isolated by column chromatography using an ethyl acetate:toluene system in a ratio of 5:1 (*v*/*v*). In this way, product **3** was obtained in the form of a yellow resin with a yield of 73%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.31 (t, *J* = 6.0 Hz, 1H, NH), 7.71–7.77 (m, 6H, Ph), 7.64–7.68 (m, 5H, Ph), 7.56–7.61 (m, 6H, Ph), 7.40–7.49 (m, 6H, Ph), 7.30–7.35 (m, 2H, Ph), 5.42 (d, *J* = 4.6 Hz, 2H, CH_2), 5.10 (d, *J* = 6.8 Hz, 2H, CH_2); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ 170.4, 166.3, 132.4 (d, *J* = 3.0 Hz), 131.6 (d, *J* = 9.1 Hz), 130.6, 129.5, 129.3, 128.4, 127.6 (d, *J* = 12.1 Hz), 126.0, 125.8, 125.0, 124.9, 115.0 (d, *J* = 84.8 Hz), 54.0, 40.5 (d, *J* = 62.6 Hz); ^{31}P{^{1}H}-NMR (161.9 MHz, $CDCl_3$): δ 19.4 (s) ppm; IR (ATR): 3398, 3063, 1660, 1580, 1529, 1488, 1439, 1283, 1109, 1061, 997, 727, 690 cm^{-1}; HRMS (ESI) *m*/*z*: calculated for $C_{34}H_{30}N_2O_2P$ $[M + H]^+$ 529.2045, found 529.2043.

3.3. Synthesis of [(N-benzamidomethyl)(N-benzoyl)amino]methyltriphenylphosphonium Tetrafluoroborate **3** *from N-benzoylaminomethyltriphenylphosphonium Tetrafluoroborate* **1** *in the Presence of Hünig's Base*

N-benzoylaminomethyltriphenylphosphonium tetrafluoroborate **1** (0.25 mmol, 121 mg) and acetonitrile (1 mL) were placed into a flame-dried glass vial (5 mL). After a few minutes of mixing, Hünig's base (0.313 mmol, 40.4 mg, 54.4 μL) was added. The vial was purged with argon and sealed with a screw-cup. The reaction was carried out at 80 °C for 10 h. The main product **3** was isolated by column chromatography using an ethyl acetate:toluene system in a ratio of 5:1 (*v*/*v*). In this way, product **3** was obtained in the form of a yellow resin with a yield of 62%.

3.4. Reaction of N-benzoylaminomethyltriphenylphosphonium Tetrafluoroborate **1** *and Benzaldehyde in the Presence of Base*

N-benzoylaminomethyltriphenylphosphonium tetrafluoroborate **1** (0.25 mmol, 121 mg), benzaldehyde (1.0 mmol, 106.1 mg, 102 μL), and the solvent (THF or CH_3CN, 1 mL) were placed into a flame-dried glass vial (5 mL). After a few minutes of mixing, the base (Et_3N, LDA, *t*-BuOK, or DIPEA) was added. The vial was purged with argon and sealed with a screw-cup. The reaction was carried out under the conditions given in Scheme 1 and its progress was monitored by NMR.

4. Conclusions

The synthesis of [(*N*-benzamidomethyl)(*N*-benzoyl)amino]methyltriphenylphosphonium tetrafluoroborate from *N*-benzoylaminomethyltriphenylphosphonium tetrafluoroborate

in the presence of DIPEA was described. It proceeds smoothly at room or elevated temperature (80 °C) in CH_3CN. For the first time, an amidoalkylation reaction was noticed in which the *N*-acylaminomethylphosphonium salt is both a precursor of the amidoalkylating agent and the nucleophile.

Supplementary Materials: Supporting information includes ^{1}H-, ^{13}C-, ^{31}P-NMR, IR, and MS spectra of the compound **3**.

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Data Availability Statement: The data presented in this study are available on request from the corresponding authors.

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Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Neto, B.A.D.; Rocha, R.O.; Rodrigues, M.O. Catalytic Approaches to Multicomponent Reactions: A Critical Review and Perspectives on the Roles of Catalysis. *Molecules* **2022**, *27*, 132. [CrossRef] [PubMed]
2. Marcantoni, E.; Palmieri, A.; Petrini, M. Recent synthetic applications of α-amido sulfones as precursors of N-acylimino derivatives. *Org. Chem. Front.* **2019**, *6*, 2142–2182. [CrossRef]
3. Vinogradov, M.G.; Turova, O.V.; Zlotin, S.G. The progress in the chemistry of *N*-acyliminium ions and their use in stereoselective organic synthesis. *Russ. Chem. Rev.* **2017**, *86*, 1–17. [CrossRef]
4. Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. Catalytic Asymmetric Reactions with N,O-Aminals. *ACS Catal.* **2016**, *6*, 5747–5763. [CrossRef]
5. Aranzamendi, E.; Arrasate, S.; Sotomayor, N.; González-Díaz, H.; Lete, E. Chiral Brønsted Acid Catalyzed Enantioselective α-Amidoalkylation Reactions: A Joint Experimental and Predictive Study. *ChemistryOpen* **2016**, *5*, 540–549. [CrossRef] [PubMed]
6. Schneider, A.E.; Manolikakes, G. $Bi(OTf)_3$-Catalyzed Multicomponent α-Amidoalkylation Reactions. *J. Org. Chem.* **2015**, *80*, 6193–6212. [CrossRef]
7. Kataja, A.O.; Masson, G. Imine and iminium precursors as versatile intermediates in enantioselective organocatalysis. *Tetrahedron* **2014**, *70*, 8783–8815. [CrossRef]
8. Mazurkiewicz, R.; Październiemiok-Holewa, A.; Adamek, J.; Zielińska, K. α-Amidoalkylating agents: Structure, synthesis, reactivity and application. *Adv. Heterocycl. Chem.* **2014**, *111*, 43–94. [CrossRef]
9. Yazici, A.; Pyne, S.G. Intermolecular addition reactions of *N*-acyliminium ions (Part I). *Synthesis* **2009**, 339–368. [CrossRef]
10. Yazici, A.; Pyne, S.G. Intermolecular addition reactions of *N*-acyliminium ions (Part II). *Synthesis* **2009**, 513–541. [CrossRef]
11. Petrini, M. α-Amido Sulfones as Stable Precursors of Reactive *N*-Acylimino Derivatives. *Chem. Rev.* **2005**, *105*, 3949–3977. [CrossRef] [PubMed]
12. Katritzky, A.R.; Lan, X.; Yang, J.Z.; Denisko, O.V. Properties and Synthetic Utility of *N*-Substituted Benzotriazoles. *Chem. Rev.* **1998**, *98*, 409–548. [CrossRef] [PubMed]
13. Zaugh, H.E. α-Amidoalkylation at Carbon: Recent Advances—Part I. *Synthesis* **1984**, 85–110. [CrossRef]
14. Zaugg, H.E. α-Amidoalkylation at Carbon: Recent Advances—Part II. *Synthesis* **1984**, 181–212. [CrossRef]
15. Speckamp, W.N.; Hiemstra, H. Intramolecular reactions of *N*-acyliminium intermediates. *Tetrahedron* **1985**, *41*, 4367–4416. [CrossRef]
16. Hiemstra, H.; Speckamp, W.N. *N*-Acyliminium Ions as Intermediates in Alkaloid Synthesis. *Alkaloids* **1988**, *32*, 271–339. [CrossRef]
17. Zaugg, H.E. Recent Synthetic Methods Involving Intermolecular alpha-Amidoalkylation at Carbon. *Synthesis* **1970**, 49–73. [CrossRef]
18. Adamek, J.; Grymel, M.; Kuźnik, A.; Październiemiok-Holewa, A. 1-Aminoalkylphosphonium Derivatives: Smart Synthetic Equivalents of *N*-Acyliminium-Type Cations, and Maybe Something More: A Review. *Molecules* **2022**, *27*, 1562. [CrossRef]
19. Adamek, J.; Węgrzyk, A.; Kończewicz, J.; Walczak, K.; Erfurt, K. 1-(*N*-Acylamino)alkyltriarylphosphonium Salts with Weakened C_α-P^+ Bond Strength—Synthetic Applications. *Molecules* **2018**, *23*, 2453. [CrossRef]
20. Mazurkiewicz, R.; Grymel, M. Reaction of *N*-Acyl-α-triphenylphosphonio-α-amino Acid Esters with Organic Bases: Mechanism of the Base-Catalyzed Nucleophilic Substitution of the Triphenylphosphonium Group. *Monatsh. Chem.* **2002**, *133*, 1197–1204. [CrossRef]

21. Mazurkiewicz, R.; Kuźnik, A.; Grymel, M.; Kuźnik, N. *N*-Acyl-α-triphenylphosphonioglycinates in the Synthesis of α,β-Dehydro-α-amino Acid Derivatives. *Monatsh. Chem.* **2004**, *135*, 807–815. [CrossRef]
22. Adamek, J.; Zieleźny, P.; Erfurt, K. *N*-protected 1-aminoalkylphosphonium salts from amides, carbamates, lactams, or imides. *J. Org. Chem.* **2021**, *86*, 5852–5862. [CrossRef] [PubMed]