JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

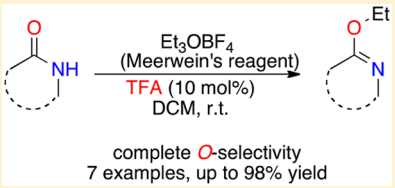
Synthesis of Imidates: TFA-Mediated Regioselective Amide Alkylation Using Meerwein's Reagent

Kirill Popov and Peter Somfai*

Centre for Analysis and Synthesis, Department of Chemistry, Lund University, P.O. Box 124, 221 00 Lund, Sweden

Supporting Information

ABSTRACT: Regioselective *O*-alkylation of an amide to form the corresponding imidate is a common synthetic problem, often resulting in varying amounts of *N*-alkylation. Screening existing methods for converting amides to imidates gave inconsistent or irreproducible results, sometimes affording *N*-alkylamide as the major product. A simple and reliable protocol for amide *O*-alkylation with complete regioselectivity has been designed, and its scope and efficiency demonstrated on a number of substrates.

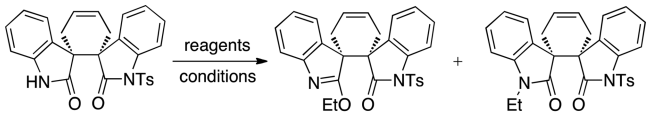


Imidates, also known as imino ethers, are potent electrophiles in contrast to the corresponding amides.[1] Therefore, imidate formation is often viewed as a way to activate the otherwise relatively inert or unreactive amide or nitrile functionalities. Application of the imidates in synthesis includes hydrolysis to esters, reactions with nucleophiles, such as alcohols or amines to form *ortho*-esters or amidines, respectively, as well as the synthesis of a wide variety of heterocyclic compounds.[2]

The are several methods to form an imidate such as the Pinner reaction (acid-catalyzed alcoholysis of a nitrile)[3] and synthesis from *ortho*-esters[4] or carbonyl compounds, the most common being direct alkylation of amides.[5] The latter method, however, has an intrinsic issue relating to the competition between *N*- and *O*-alkylation. *N*-Alkylation is commonly achieved under basic conditions (NaH, LHMDS, K_2CO_3) in polar solvents, using an alkyl halide, although the *O*-alkylation byproduct is often observed due to equilibration of the amide anion.[6] When *O*-alkylation is desired there are several possibilities, including treating an amide with dimethyl sulfate,[7] diazomethane,[8] or trialkyloxonium tetrafluoroborates (Meerwein's reagent),[9] most often in combination with a hindered base such as iPr_2EtN.[10−12]

While developing a total synthesis of a dehaloperophoramidine,[13] we needed to synthesize imidate **2** in order to activate the amide moiety in compound **1** for a subsequent nucleophilic attack (Table 1). To our distress, using published methods specifically designed for *O*-selective amide alkylation (Et_3OBF_4, CH_2Cl_2, amine base) consistently afforded mixtures of *N*- and *O*-alkylation products (**2**: **3**) in varying ratios. In order to resolve the problem, we decided to carefully screen the reaction conditions. When the alkylation was run using a newly opened bottle of Et_3OBF_4, a poor *N*/*O* alkylation ratio favoring the imidate **2** was obtained (entry 1), while the use of an old bottle (≥6 months) gave **2** as the major product (entry 2). Screening of various amines clearly revealed that the sterically hindered DTBMP (2,6-di-*tert*-butyl-4-methylpyridine) delivered **2** in the highest selectivity and that both Et_3N and iPr_2EtN actually favored *O*-alkylation while still generating

Table 1. Alkylation of Amide 1 Using $Et_3O{\cdot}BF_4$



1 2 3

entry	reagents	conditions	ratio **2**:**3**[a]	yield (**2** + **3**) (%)
1	$Et_3O{\cdot}BF_4$ (2 equiv, fresh batch)	CH_2Cl_2, rt	65:35	90
2	$Et_3O{\cdot}BF_4$ (5 equiv, old batch)	CH_2Cl_2, rt	90:10	87
3	$Et_3O{\cdot}BF_4$ (2 equiv), Et_3N (3 equiv)	CH_2Cl_2, 0 °C→ rt	75:25	80
4	$Et_3O{\cdot}BF_4$ (2 equiv), i-Pr_2EtN (3 equiv)	CH_2Cl_2, 0 °C→ rt	60:40	89
5	$Et_3O{\cdot}BF_4$ (2 equiv), DTBMP (3 equiv)	CH_2Cl_2, 0 °C→ rt	85:15	92
6	$Et_3O{\cdot}BF_4$ (2 equiv), TFA (10 mol %)	CH_2Cl_2, rt	100:0	98

[a]Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture.

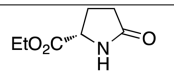
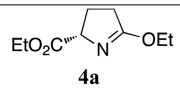
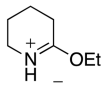
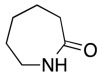
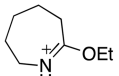
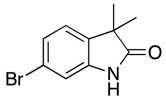
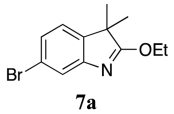
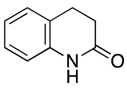
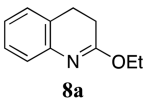
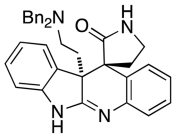
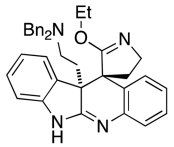
considerable amounts of **3** (entries 3−5). From these experiments, it was clear that using an old bottle of Et_3OBF_4 gave the highest selectivity for the desired imidate **2**. We speculated that this might be due to the formation of minute amounts of acid, as a result of Et_3OBF_4 hydrolysis, and we decided to perform the reaction with TFA (entry 6). Gratifyingly, this procedure delivered imidate **2** as the sole isomer in excellent yield, irrespective of the quality of the Meerwein's reagent.

Having identified the TFA mediated protocol we decided to screen a number of amides (**4**−**9**) in order to investigate the scope of the methodology (Table 2). We found that treating a

Received: February 26, 2016
Published: March 28, 2016

DOI: 10.1021/acs.joc.6b00424
J. Org. Chem. 2016, 81, 3470−3472

Table 2. Amide Alkylation in the Presence of 10 mol % of TFA[a,b]

entry	amide	product	yield
1	 **4**	 **4a**	97%
2	 **5**	 **5a**	85%
3	 **6**	 **6a**	91%
4	 **7**	 **7a**	97%
5	 **8**	 **8a**	94%
6[c]	 **9**	 **9a**	72%

[a]See the general procedure in the Experimental Section. [b]Using 5−20 mol % of TFA gave identical results. [c]Reaction time 24 h.

solution of the substrate in dry CH_2Cl_2 with 10 mol % of TFA followed by addition of the oxonium salt at room temperature in all cases leads to the corresponding imidate (**4a**−**9a**) in high yield and complete regioselectivity; no *N*-alkylation byproduct was detected by ^{1}H NMR spectroscopic investigation of the crude reaction mixture.

Imidate **9a** was a potential intermediate in our studies toward the total synthesis of dehaloperophoramidine,[13] and its formation from amide **9** was of particular interest (entry 6). The alkylation of **9** using $Et_3O{\cdot}BF_4$ raises several issues concerning chemoselectivity as the tertiary amine moiety, the amidine functionality and the amide can all be alkylated by the powerful electrophilic reagent. Indeed, when compound **9** was treated with Me_3OBF_4 in CH_2Cl_2 under basic conditions (DTBMP or iPr_2EtN) complex mixtures were obtained, presumably containing the products derived from quaternization of the tertiary amine, and alkylations of the amidine and amide moieties. In contrast to this, when we treated amide **9** with TFA (3 equiv) followed by addition of the electrophile, imidate **9a** was formed as a single isomer in good yield. In this case, TFA not only facilitates the *O*-alkylation of the lactam but also serves as an in situ protecting group for the tertiary amine and amidine functionalities. Although the mechanism for the high *O*-selectivity obtained in this TFA mediated amide alkylation remains unclear, the reliability of the method is highly desirable.

In conclusion, we have developed a simple and practical protocol for synthesis of imidates from amides using trialkyloxonium tetrafluoroborates in the presence of catalytic amounts of TFA, delivering the products in high yield and with complete selectivity.

EXPERIMENTAL SECTION

All of the air- and/or moisture-sensitive reactions were conducted under a nitrogen atmosphere. Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise indicated. Reagents were purchased from commercial sources of the highest quality and used without further purification unless stated otherwise. Reactions were monitored by thin-layer chromatography or mass spectrometry. The NMR spectra of all the compounds are provided in the Supporting Information.

General Procedure for the Alkylation of 1 with $Et_3O{\cdot}BF_4$ (No Additive). To an ice-cold solution of **1** (0.47 g, 1.00 mmol) in dry CH_2Cl_2 (25 mL) was slowly added $Et_3O{\cdot}BF_4$ (0.38 g, 2.00 mmol, newly opened bottle or old bottle). The reaction was allowed to slowly warm to rt and was stirred at that temperature for 12 h. The reaction was then quenched with H_2O (50 mL), washed with satd aq $NaHCO_3$ (3 × 10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to yield a mixture of **2** and **3** which was analyzed by NMR to determine the ratio.

General Procedure for the Alkylation of 1 with $Et_3O{\cdot}BF_4$ under Basic Conditions. To an ice-cold solution of **1** (0.47 g, 1.00 mmol) and the corresponding base (3 mmol) in dry CH_2Cl_2 (25 mL) was slowly added $Et_3O{\cdot}BF_4$ (0.38 g, 2.00 mmol). After being stirred for 2 h, the reaction was allowed to warm to rt and was stirred at that temperature for additional 12 h. The reaction was then quenched with H_2O (50 mL), washed with brine (30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afforded a mixture of **2** and **3** which was analyzed by NMR to determine the ratio.

General Procedure for the Alkylation of Amides with $Et_3O{\cdot}BF_4$ in the Presence of Catalytic TFA. To a solution of amide (1.00 mmol) and TFA (10 mol %, 76 μL, 0.10 mmol) in dry CH_2Cl_2 (7 mL) was slowly added $Et_3O{\cdot}BF_4$ (190 mg, 1.20 mmol) at rt. The reaction was allowed to slowly warm to rt and was stirred at that temperature for 12 h. Removal of solvent affords the corresponding imidate tetrafluoroborate salt. In case a free base imidate is desired, the reaction was then quenched with H_2O (5 mL), washed with NaOH (1 M, 2 × 1 mL) and brine (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried ($MgSO_4$) and concentrated to afforded the corresponding free base imidate.

(2′S,3R*)-2-Ethoxy-1″-tosyldispiro[indole-3,1′-cyclohexane-2′,3″-indolin]-4′-en-2″-one (**2**).*[13] Light yellow amorphous solid (488 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$, 0 °C): δ 7.99 (d, *J* = 7.9 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.47−7.40 (m, 2H), 7.34−7.30 (m, 2H), 7.20 (d, *J* = 9.0 Hz, 2H), 7.17−7.11 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.68 (t, *J* = 7.7 Hz, 1H), 6.07 (br s, 1H), 5.88 (br s, 1H), 5.67 (d, *J* = 7.7 Hz, 1H), 4.27−4.13 (m, 2H), 3.32 (d, *J* = 18.3 Hz, 1H), 2.67 (d, *J* = 19.5 Hz, 1H), 2.42 (s, 3H), 2.14−2.04 (m, 1H), 2.03−1.94 (m, 1H), 1.29−1.24 (m, 4H).

*(S)-Ethyl 5-Ethoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (**4a**).* Colorless oil (179 mg, 97%, lit.[14] yellow oil, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52−4.30 (m, 1H), 4.26−3.89 (m, 5H), 2.61−2.33 (m, 2H), 2.28−1.92 (m, 3H), 1.35−1.01 (m, 7H).

*6-Ethoxy-2,3,4,5-tetrahydropyridine HBF_4 Salt (**5a**).* Colorless semisolid (108 mg, 85%, lit.[15] white solid, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.2 (br s., 1H), 4.40 (q, *J* = 6.8 Hz, 2H), 3.65 (m, 2H), 2.68 (m, 2H), 1.91 (m, 4H), 1.44 (t, *J* = 6.8 Hz, 3H).

*7-Ethoxy-3,4,5,6-tetrahydro-2H-azepine HBF_4 Salt (**6a**).* Colorless semisolid (128 mg, 91%, lit.[15] white solid, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (br s., 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 3.67 (m, 2H), 2.79 (m, 2H), 1.71−1.84 (m, 6H), 1.43 (t, *J* = 7.0 Hz, 3H).

*6-Bromo-2-ethoxy-3,3-dimethyl-3H-indole (**7a**).*[16] Red amorphous solid (260 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49

DOI: 10.1021/acs.joc.6b00424
J. Org. Chem. 2016, 81, 3470−3472

(d, J = 3.5 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 4.48 (q, J = 6.9 Hz, 2H), 1.44 (t, J = 6.9 Hz, 3H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.8, 153.5, 141.6, 125.9, 122.2, 121.6, 120.9, 65.4, 47.8, 24.2, 23.2, 14.3. HRMS (EI) for $C_{12}H_{14}BrNO$: calcd [M^+] 267.0259, found 267.0263.

*2-Ethoxy-3,4-dihydroquinoline (**8a**).*[17] Colorless oil (164 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.19 (m, 1H), 7.14 (td, J = 7.2, 1.5 Hz, 0H), 4.49 (q, J = 7.1 Hz, 1H), 2.97 (t, J = 8.2 Hz, 1H), 2.67−2.39 (m, 1H), 1.48 (t, J = 7.1 Hz, 2H).

*N,N-Dibenzyl-2-((3′R,10bS)-2′-Ethoxy-4′,5′,6,10b-tetrahydrospiro[indolo[2,3-b]quinoline-11,3′-pyrrole]-10b-yl)-ethanamine (**9a**).* White amorphous solid (389 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89−7.08 (m, 18H), 4.47−4.59 (m, 2H), 3.27−3.42 (m, 5H), 3.09−3.15 (m, 1H), 2.17−2.34 (m, 3H), 1.70−1.88 (m, 3H), 1.53 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 170.6, 153.5, 139.4, 138.4, 133.4, 128.2, 128.0, 126.6, 123.5, 122.8, 118.0, 115.2, 64.6, 57.9, 54.6, 51.6, 48.2, 36.6, 28.8, 14.8. HRMS (EI) for $C_{36}H_{36}N_4O$: calcd [M^+] 540.2889, found 540.2892.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00424.

NMR spectra for all new and known compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: peter.somfai@chem.lu.se.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Swedish Research Council, the Carl Tryggers Foundation, the Crafoord Foundation, the Swedish Institute and Lund University.

■ REFERENCES

(1) Nelson, D. G. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley: New York, 1975; pp 385−489.
(2) Roger, R.; Neilson, D. *Chem. Rev.* **1961**, *61*, 179−211.
(3) Caron, S.; Wei, L.; Douville, J.; Ghosh, A. *J. Org. Chem.* **2010**, *75*, 945−947.
(4) Roberts, R. M. *J. Am. Chem. Soc.* **1949**, *71*, 3848−3849.
(5) Challis, B. C.; Challis, J. A. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley Interscience: London, 1970; p 731.
(6) Levine, R.; Fernelius, W. C. *Chem. Rev.* **1954**, *54*, 449−573.
(7) Petersen, S.; Tietze, E. *Chem. Ber.* **1957**, *90*, 909−921.
(8) Bartels, G.; Hinze, R.-P.; Wullbrandt, D. *Liebigs Ann. Chem.* **1980**, *1980*, 168−170.
(9) Meerwein, H.; Hinz, G.; Hofmann, P.; Kroning, E.; Pfeil, E. *J. Prakt. Chem.* **1937**, *147*, 257−285.
(10) Raber, D. J.; Gariano, P.; Brod, A. O.; Gariano, A.; Guida, W. C.; Guida, A. R.; Herbst, M. D. *J. Org. Chem.* **1979**, *44*, 1149−1154.
(11) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068−5069.
(12) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794−13795.
(13) Popov, K.; Hoang, A.; Somfai, P. *Angew. Chem., Int. Ed.* **2016**, *55*, 1801−1804.
(14) Berry, J. M.; Doyle, P. M.; Young, D. W. *Tetrahedron* **2005**, *61*, 287−299.
(15) Menezes, R.; Smith, M. B. *Synth. Commun.* **1988**, *18*, 1625−1636.
(16) Atwal, K. S.; Ferrara, F. N.; Ding, C. Z.; Grover, G. J.; Sleph, P. G.; Dzwonczyk, S.; Baird, A. J.; Normandin, D. E. *J. Med. Chem.* **1996**, *39*, 304−313.
(17) Golovko, T. V.; Soloveva, N. P.; Anisimova, O. S.; Granik, V. G. *Chem. Het. Comp.* **2003**, *39*, 344−353.

DOI: 10.1021/acs.joc.6b00424
J. Org. Chem. 2016, 81, 3470−3472