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September 2014: The paragraphs above replace the section “Handling and Disposal of Hazardous Chemicals” in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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SYNTHESIS OF PYRAZOLO[1,5-a]PYRIDINES VIA AZIRINES:
PREPARATION OF 2-(3-BROMOPHENYL)-6-(TRIFLUOROMETHYL)PYRAZOLO[1,5-a]PYRIDINE

A. \[
\begin{align*}
\text{Br} & \quad \text{Cl} \\
\begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\quad \text{CF}_3
\end{align*}
\]

\[+\]

\[
\begin{align*}
\text{NaH} \\
\text{THF, 60 °C}
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\begin{array}{c}
\text{N} \\
\text{CF}_3
\end{array}
\quad \text{CF}_3
\end{align*}
\]

B. \[
\begin{align*}
\text{Br} & \quad \text{O} \\
\begin{array}{c}
\text{N} \\
\text{CF}_3
\end{array}
\quad \text{CF}_3
\end{align*}
\]

\[+\]

\[
\begin{align*}
\text{HONH}_2\cdot\text{HCl} \\
\text{NaOH, MeOH} \\
\text{rt to 70 °C}
\end{align*}
\]

C. \[
\begin{align*}
\text{Br} & \quad \text{O} \\
\begin{array}{c}
\text{N} \\
\text{CF}_3
\end{array}
\quad \text{CF}_3
\end{align*}
\]

\[+\]

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{O} \\
\begin{array}{c}
\text{O} \\
\text{CF}_3
\end{array}
\quad \text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2 \\
\text{0 °C to rt}
\end{align*}
\]

D. \[
\begin{align*}
\text{Br} & \quad \text{N} \\
\begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\quad \text{CF}_3
\end{align*}
\]

\[+\]

\[
\text{microwave} \\
175 °C
\]

Checked by Hiroshi Nakagawa and Jonathan A. Ellman.

Caution! Hydroxylamine hydrochloride explodes with heating above 110 °C.

1. Procedure

A. 1-(3-Bromophenyl)-2-[5-(trifluoromethyl)-2-pyridinyl]ethanone (1). A 2-L, oven-dried, three-necked, round-bottomed flask equipped with two stoppers and nitrogen inlet is charged with sodium hydride (13.2 g, 330
mmol, 60% dispersion in oil) and a magnetic stir bar (Note 1). Hexanes (300 mL) (Note 2) are added, and the suspension is stirred, allowed to settle, and the supernatant (250 mL) is poured off by decantation. Dry THF (300 mL) (Note 3) is added to the flask, and a reflux condenser with nitrogen inlet, a thermometer, and a rubber septum are attached. A solution of 3’-bromo-acetophenone (30.0 g, 20 mL, 151 mmol) (Note 4) in dry THF (60 mL) is added over 5 min via syringe to the sodium hydride suspension. The resulting light brown suspension is stirred for 5 min, and a solution of 2-chloro-5-(trifluoromethyl)pyridine (24.9 g, 137 mmol) (Note 5) in dry THF (60 mL) is added over 10 min via syringe. Additional dry THF (120 mL) is used to rinse the sides of the flask. The resulting orange-brown solution is heated in an oil bath until the internal temperature is 60 °C. The solution darkens in color as the reaction proceeded. After stirring for 24 h, the reaction solution is cooled to room temperature. Only trace starting material remains as determined by TLC: product (1) $R_f = 0.5$ (4:1 hexanes:ethyl acetate). To allow more volume during quenching, the mixture is transferred equally into two 1-L Erlenmeyer flasks. To each portion is added brine (150 mL) (Note 6) and ethyl acetate (150 mL). After the reaction is safely quenched, all material is transferred to a 2-L separatory funnel. The aqueous layer is removed and the organic layer is washed with additional brine (100 mL). The combined aqueous layers are extracted with ethyl acetate (100 mL), and the combined organic layers are washed with MgSO$_4$ (150 g). The drying agent is filtered off and washed with additional ethyl acetate (200 mL). The combined filtrate is concentrated in vacuo (40 °C, 20 mmHg). Celite (24 g) and methylene chloride (50 mL) are added to the resulting brown solid and concentrated by rotary evaporation (35 °C, 20 mmHg). The adsorbed material is loaded onto a column and purified by silica gel chromatography (330 g silica gel, 25 cm x 6 cm, start 10:1 hexanes:ethyl acetate to 3:1 gradient, 100 mL/min, 30 min, 3 L total solvent volume) to give product 1 (37.5 g, 79%) as a bright yellow solid (Note 7).

B. (1Z)-1-(3-bromophenyl)-2-[5-(trifluoromethyl)-2-pyridinyl]-ethanone oxime (2). A 500-mL, three-necked, round-bottomed flask equipped with a thermometer and a mechanical stirrer is charged with ketone (1) (15.0 g, 43.7 mmol). Methanol (120 mL) (Note 8) is added, followed by slow addition of aqueous sodium hydroxide (2.5 M, 75 mL, 188 mmol) (Note 9) over 5 min, which completely dissolved the ketone to give an orange solution. Hydroxylamine hydrochloride (15.2 g, 219 mmol) (Note 10) is added in small portions over 15 min, during which the solution
changed from orange to bright yellow (Note 11). An additional 10 mL of methanol is used to wash down the sides of the flask. Vigorous stirring is required due to the large quantity of solids present. A reflux condenser is attached and the reaction mixture is heated in an oil bath until the internal temperature is 70 °C. The solids dissolved and the bright yellow color faded as the reaction proceeded. Once an internal temperature of 70 °C is reached, the reaction mixture is stirred for 90 min at which point only trace starting material remained as determined by TLC: product (2) $R_f = 0.33$ (4:1 hexanes:ethyl acetate). The oil bath is removed, the reaction solution cooled to room temperature over 30 minutes, and a solid precipitated out of solution (Note 12). The reaction mixture is further cooled to 0 °C in an ice bath for 30 min, and all of the white solid material is collected by filtration using a fritted funnel (9 cm, 350 mL, M). The solid is washed with cold water (3 x 20 mL) and is dried under high vacuum (<1 mmHg) at 50 °C for 5 hours. The pale yellow solid is dissolved in methanol (75 mL) at 60 °C and water (25 mL) is added slowly at 60 °C until the solution became cloudy. The solution is cooled to room temperature over 1 h and the precipitate that formed is filtered using a fritted funnel (9 cm, 350 mL, M). The solid is washed with cold water (3 x 20 mL) and dried under high vacuum (<1 mmHg, 50 °C) overnight to give (2) as pale yellow solid (11.4 g, 72%) (Notes 13, 14).

C. 2-[3-(3-Bromophenyl)-2H-azirin-2-yl]-5-(trifluoromethyl)pyridine (3). A 250-mL, oven-dried, three-necked, round-bottomed flask equipped with nitrogen inlet, a thermometer, a rubber septum, and a magnetic stir bar is charged with oxime (2) (12.0 g, 33.4 mmol) and dry dichloromethane (50 mL) (Note 15). The cloudy yellow solution is cooled in an ice bath and triethylamine (18.6 mL, 133 mmol) (Note 16) is added dropwise over 10 min via syringe. Following the triethylamine addition, all solids had dissolved, and stirring is continued at 0 °C for 15 min. Trifluoroacetic anhydride (5.7 mL, 41 mmol) (Note 17) is then added dropwise over 10 min via syringe (Note 18). The solution darkened in color as the reaction proceeded. After 30 min of stirring, the flask is allowed to warm to room temperature and stirring is continued for an additional 60 min. Only trace starting material remained as determined by TLC: product (3) $R_f = 0.25$ (9:1 hexanes:ethyl acetate). The reaction is then quenched by the addition of water (20 mL). The aqueous layer is extracted with methylene chloride (2 x 15 mL), and the combined organic layers are dried over MgSO$_4$ (20 g), filtered, and concentrated (35 °C, 20 mmHg). Celite (10 g) and methylene
chloride (40 mL) are added to the resulting dark red oil and concentrated by rotary evaporation (35 °C, 20 mmHg). The adsorbed material is loaded onto a column and purified using silica gel chromatography (330 g silica gel, 25 cm x 6 cm, start 20:1 hexanes:ethyl acetate to 5:1 gradient, 100 mL/min, 30 min, 3 L total solvent volume) to give (3) as a dark orange oil (8.61 g 76%) (Note 19).

D. 2-(3-Bromophenyl)-6-(trifluoromethyl)pyrazolo[1,5-a]pyridine (4). A 20-mL microwave vial is charged with azirine (3) (2.20 g, 6.45 mmol) dissolved in 1,2-dichloroethane (11 mL) (Note 20). A stir bar is added, the vial is sealed, and the resulting orange solution is heated for 1 h in a Biotage Initiator Eight Microwave Reactor held at a constant temperature of 175 °C (Notes 21, 22). Only trace starting material remained as determined by TLC: product (4) Rf = 0.35 (9:1 hexanes:ethyl acetate). A total of 6.60 g (3 x 2.20 g, 19.3 mmol) of (3) is treated in this manner and the resulting solutions are combined and concentrated in vacuo (40 °C, 20 mmHg). Celite (7 g) and methylene chloride (40 mL) are added and concentrated by rotary evaporation (35 °C, 20 mmHg). The adsorbed material is loaded onto a column and purified using silica gel chromatography (120 g silica gel, 25 cm x 3 cm, start 20:1 hexanes:ethyl acetate to 3:1 gradient, 40 mL/min, 30 min, 1.2 L total solvent volume) to give (4) (6.08 g, 92%) as a yellow powder (Notes 23, 24).

2. Notes

1. Sodium hydride (dispersion, 60% in oil) was purchased from the Aldrich Chemical Company, Inc. and was used as received. When using 60% dispersions, the submitters have found the need to add 1.2 equiv. Consequently for the chemistry of Step A the submitters have found that the reaction proceeds to completion more reliably with a total of 2.4 equiv of NaH.

2. Hexanes (HPLC Grade) was purchased from EMD and was used as received.

3. Drisolv® THF (99.9%) was purchased from EMD and was used as received.

4. 3’-Bromo-acetophenone (99%) was purchased from the Aldrich Chemical Company, Inc. and was used as received.

5. 2-Chloro-5-(trifluoromethyl)pyridine was purchased from the Aldrich Chemical Company, Inc. and was used as received.
6. Aqueous saturated brine solution was added dropwise to minimize the exotherm.

7. Submitters made proton and carbon assignments using 2D NMR and found product 1 exists as an approximate 7:3 keto/enol tautomeric mixture: mp 85–86 °C; IR (film) cm⁻¹ 1603, 1547, 1477, 1323, 1259, 1161, 1116, 1075, 1058; TLC: Rf = 0.52 (silica gel, 4:1 hexanes:ethyl acetate); ¹H NMR (400 MHz, DMSO-d₆) δ: 4.71 (s, 0.5 H), 6.58 (s, 0.75 H), 7.39 (m, 1.5 H), 7.49 (t, 0.25 H, J = 8.0 Hz), 7.62 (m, 1 H), 7.82 (m, 1 H), 7.98 (m, 1 H), 8.07 (d, 0.75 H, J = 8.0 Hz), 8.14 (m, 0.5 H), 8.74 (br s, 0.75 H), 8.85 (br s, 0.25 H), 14.97 (br s, 0.75 H); ¹³C NMR (100 MHz, DMSO-d₆) δ: 47.8, 94.9, 120.0 (q), 122.5, 122.6, 122.7, 122.9, 123.6, 124.0, 124.9, 125.4, 127.8, 128.1, 128.5, 131.1, 131.2, 131.4, 133.2, 134.2 (q), 134.9 (q), 136.5, 138.2, 138.7, 142.3 (q), 146.1 (q), 160.6, 164.9, 195.9; ¹⁹F NMR (376 MHz, DMSO-d₆) δ: −60.03, −60.06; LRMS (ESI) m/z (%): 344 (100), 345 (17), 346 (100), 347 (17); HRMS (FAB) m/z M⁺ calcd for C₁₄H₉BrF₃NO: 342.9820. Found: 342.9825. Anal. Calcd for C₁₄H₉BrF₃NO: C, 48.86; H, 2.64; N, 4.07. Found: C, 48.82; H, 2.69; N, 4.07.

8. Methanol was purchased from EMD and was used as received.

9. Sodium hydroxide (2.50 ± 0.02 M) was purchased from VWR and was used as received.

10. Hydroxylamine hydrochloride (98%) was purchased from the Aldrich Chemical Company, Inc. and was used as received.

11. The submitters found that extended reaction time is required when less than 5 equiv of hydroxylamine hydrochloride is used. For example, 3 equiv of hydroxylamine hydrochloride required 24 h at 70 °C to reach completion. In addition, test reactions demonstrated that the use of at least 2.5 equiv of hydroxylamine hydrochloride was necessary for the reaction to reach completion.

12. The submitters obtained a white flocculent solid (12.0 g, 76%) out of the reaction solution, which was used without purification in the next step.

13. The oxime (2) exhibits the following characteristics: mp 123–125 °C; IR (film) cm⁻¹ 3002, 2835, 1610, 1324, 1176, 1164, 1127, 1081, 1059, 1028; TLC: Rf = 0.33 (silica gel, 4:1 hexanes:ethyl acetate); ¹H NMR (400 MHz, DMSO-d₆) δ: 4.35 (s, 2 H), 7.30 (t, 1 H, J = 8.0 Hz), 7.52 (m, 2 H), 7.68 (d, 1 H, J = 8.0 Hz), 7.87 (s, 1 H), 8.08 (d, 1 H, J = 8.0 Hz), 8.83 (br s, 1 H), 11.75 (br s, 1 H); ¹³C NMR (100 MHz, DMSO-d₆) δ: 34.3, 122.2, 123.8, 125.5, 128.9, 131.0, 131.9, 134.5 (q), 138.7, 146.2 (q), 152.6, 162.5; ¹⁹F NMR (376 MHz, DMSO-d₆) δ: −59.99; LRMS (ESI) m/z (%): 359 (100),
360 (17), 361 (100), 362 (17); HRMS (FAB) m/z [M+H]+ calcd for C_{14}H_{11}BrF_{3}N_{2}O: 359.0005 found: 359.0006. Anal. Calcd for C_{14}H_{10}BrF_{3}N_{2}O: C, 46.82; H, 2.82; N, 7.80. Found: C, 46.55; H, 2.68; N, 7.67.

14. The submitters reported yields that ranged from 65-81% for this step, with decreasing returns as the reaction scale was increased. The submitters also reported that the oxime (2) could be efficiently converted back to ketone (1) by treatment with 1:1 water:acetone and a few drops of 4M HCl at 50°C for 24 h.

15. Dry dichloromethane (99.8%) was purchased from the Aldrich Chemical Company, Inc. and was used as received.

16. Triethylamine was purchased from the Aldrich Chemical Company, Inc. and was used as received.

17. Trifluoroacetic anhydride was purchased from the Aldrich Chemical Company, Inc. and was used as received.

18. Trifluoroacetic anhydride is volatile under these conditions; the addition should be made slowly and carefully.

19. The azirine (3) exhibits the following characteristics: IR (film) cm\(^{-1}\) 1736, 1604, 1323, 1162, 1077; TLC: R\(_f\) = 0.30 (silica gel, 9:1 hexanes:ethyl acetate); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 3.63 (s, 1 H), 7.57 (t, 1 H, J = 8.0 Hz), 7.59 (d, 1 H, J = 8 Hz), 7.87 (d, 1 H, J = 8.0 Hz), 7.91 (d, 1 H, J = 8.0 Hz, 1 H), 8.07 (m, 1 H), 8.09 (dm 1 H, J = 8.0 Hz), 8.76 (s, 1 H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 35.3, 122.2, 122.9, 123.0, 123.9 (q), 125.5, 129.2, 132.1, 132.6, 134.2 (q), 136.8, 146.2 (q), 160.4, 164.4; \(^19\)F NMR (376 MHz, DMSO-\(d_6\)) \(\delta\): –60.04; LRMS (ESI) m/z (%): 341 (100), 342 (17), 343 (100), 344 (17); HRMS (FAB) m/z [M+H]+ calcd for C_{14}H_{8}BrF_{3}N_{2}: 340.9901 found: 340.9895. Anal. Calcd for C_{14}H_{8}BrF_{3}N_{2}: C, 49.29; H, 2.36; N, 8.21. Found: C, 49.37; H, 2.38; N, 7.96. The submitters observed that the product solidified over time: mp 123–125 °C;

20. 1,2-Dichloroethane (99.8%) was purchased from the Aldrich Chemical Company, Inc. and was used as received.

21. Safety precautions should always be taken with any “sealed flask” reaction. The microwave reactor has a built-in “blast shield” and an automatic shut-off when a pressure is over the instrument maximum setting. Solvent choice can be a very important factor in microwave chemistry as the vapor pressure buildup must be taken into consideration as the reaction is heated. 1,2-Dichloroethane was used in Step D because it can be heated.
high enough to facilitate the desired transformation while maintaining a safe vapor pressure.

22. The submitters reported that 1,2,4-trichlorobenzene was a suitable solvent under conventional refluxing conditions and that diglyme and 1,2,4-trichlorobenzene proved to be suitable alternatives under microwave conditions. The detailed procedure described herein provided the highest conversion and yield of the desired product. Because the microwave reactor has a maximum volume of 20 mL, the checkers ran three identical reactions of 2.2 g, and the submitters ran two identical reactions of 3.3 g. The submitters also reported that the transformation of azirine (3) to pyrazolo[1,5-a]pyridine (4) is much cleaner when the microwave is used for 1 h instead of conventional heating for longer times.

23. The pyrazolo[1,5-a]pyridine (4) exhibits the following characteristics: mp 59–60 °C; IR (film) cm⁻¹ 1647, 1460, 1334, 1321, 1157, 1112, 1076, 1052; TLC: Rf = 0.38 (silica gel, 4:1 hexanes:ethyl acetate); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 7.24 (s, 1 H), 7.35 (d, 1 H, \(J = 9.2\) Hz), 7.39 (t, 1 H, \(J = 8.0\) Hz), 7.54 (d, 1 H, \(J = 8.0\) Hz), 7.81 (d, 1 H, \(J = 9.2\) Hz), 7.95 (d, 1 H, \(J = 8.0\) Hz), 8.12 (m, 1 H), 9.26 (s, 1 H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 96.3, 115.3 (q), 119.7, 122.7, 122.7, 125.4, 125.6, 128.5 (q), 129.1, 131.4, 132.1, 134.7, 142.1, 153.6; \(^19\)F NMR (376 MHz, DMSO-\(d_6\)) \(\delta\): –59.73; LRMS (ESI) \(m/z\) (%): 341 (100), 342 (25), 343 (83), 344 (17); HRMS (FAB) \(m/z\) M⁺ calcd for C\(_{14}\)H\(_8\)BrF\(_3\)N\(_2\): 339.9823 found: 339.9827. Anal. Calc for C\(_{14}\)H\(_8\)BrF\(_3\)N\(_2\): C, 49.29; H, 2.36; N, 8.21. Found: C, 49.26; H, 2.33; N, 8.11.

24. The submitters made proton and carbon assignments based on correlations in the TOCSY, gCOSY, NOESY, gHSQC, and gHMBC experiments that fully support the structure (2D NMR data not shown).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

Azirine intermediates in the synthesis of the complex pyrazolo[1,5-a]pyridine heterocycle are utilized because the method is facile and the
intramolecular nature allows control of substituent regiochemistry on the resulting bicycle (the CF$_3$ group in 4, for example). Thermal reactions of azirines involve regioselective ring opening to form highly reactive nitrene intermediates. With appropriately substituted pyridyl azirines, the electrophilic nitrene can be intercepted by the pyridyl nitrogen to give the bicyclic pyrazolo[1,5-a]pyridine with predictable substitution patterns based on the original pyridyl substitution. The most common side products derive from nitrene dimerization. The product resulting from formal C-H insertion is rarely seen in appreciable quantity.

A wide variety of intermolecular reactions have been successfully performed to produce unsubstituted pyrazolo[1,5-a]pyridines. The intermolecular syntheses of an unsubstituted pyrazolo[1,5-a]pyridine dates back to at least 1962 when Huisgen synthesized a number of interesting heterocycles including pyrazolo[1,5-a]pyridines. Huisgen was a pioneer of heterocyclic chemistry especially the use of unsubstituted 1-aminopyridinium iodide. Intermolecular syntheses of pyrazolo[1,5-a]pyridines are perhaps more common than the intramolecular variety, but the intermolecular nature fails to control the regiochemical outcome.

Azirines themselves have attracted much research interest because they represent the smallest nitrogen-containing unsaturated heterocyclic system. Most interest stems from the influence of ring strain of the azirine on the potential for elaboration to other heterocyclic systems. As with the synthesis of the pyrazolo[1,5-a]pyridines, azirine syntheses can also be categorized into intra- and intermolecular classes. Intramolecular variants as described herein (reaction of an N-functionalized imine) are usually termed the Neber reaction based on the first synthesis of an azirine in a cycloelimination reaction under basic conditions. Other intramolecular syntheses of azirines begin with vinyl azides, isoxazoles, and oxazaphospholes. The less common intermolecular approach to the synthesis of azirines usually relies on a cycloaddition between carbenes and nitriles. Useful yields in this approach generally require stabilized phosphanylcarbenes which produce phosphorous substituted azirines.

1. Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27599-3290.
2. Department of Oncology Medicinal Chemistry, GlaxoSmithKline, 5 Moore Drive, 3.4174-4B, Research Triangle Park, North Carolina 27709; email: kls62784@gsk.com.


**Appendix**

**Chemical Abstracts Nomenclature (Registry Number)**

3’-Bromoacetophenone: 1-acetyl-3-bromobenzene; (2142-63-4)
Sodium hydride; (7646-69-7)
2-Chloro-5-(trifluoromethyl)pyridine; (52334-81-3)
Hydroxylamine hydrochloride; (5470-11-1)
Trifluoroacetic anhydride; (407-25-0)
Kirk Stevens was born in Seattle, Washington. He received his undergraduate chemistry degree from Reed College (Portland, OR) where he conducted research under Prof. Pat McDougal. He then moved to UC-Santa Barbara for graduate studies with Prof. Bruce Lipshutz working on nickel-catalyzed reactions and their use in synthesis of prenylated natural products like CoQ10. As an NIH postdoctoral fellow with Prof. Yoshito Kishi at Harvard, he was part of the team that completed the total synthesis of Spongistatin. In 1998, he joined GlaxoWellcome, now GlaxoSmithKline, and has worked primarily in oncology medicinal chemistry.

Stephen Greszler was born in Painesville, Ohio. He received his undergraduate degree in biochemistry from The Ohio State University in Columbus, where he was involved in research with Professor Sean Taylor. He then moved to The University of North Carolina at Chapel Hill, where he is currently pursuing graduate work in organic synthesis under the guidance of Professor Jeffrey S. Johnson. Stephen interned at GlaxoSmithKline in Research Triangle Park during the summer of 2007, where he worked on the pyrazolo[1,5-a]pyridine chemistry described in this account.

Hiroshi Nakagawa was born in Mie, Japan, in 1973. He received his B.S. in 1996 and M.S. in 1998 from University of Tokyo. He received his Ph.D. in 2001 under the direction of Professor Tetsuo Nagano and Professor Tsunehiko Higuchi from University of Tokyo. He has been working at Dainippon Sumitomo Pharma since 2001. In 2006, he began his visiting scholar studies at the University of California, Berkeley, in the laboratories of Professor Jonathan A. Ellman. His research interest is in the area of medicinal chemistry.
$\text{BrONCF}_3 + \text{BrONCF}_3 \xrightarrow{1} \text{BrONCF}_3 + \text{BrONCF}_3$
BrONCF3 + Br

Br

1

Br

ONCF3
Br
NNCF3 HO
2
Br
NNCF₃

Br

4
Br
NNCF₃ HO
2
BrONCF3 + Br

\[ \text{Br} \]

\[ \text{ONCF3} \]

\[ \text{Br} \]

\[ \text{OH} \]

\[ \text{N} \]

\[ \text{CF}_3 \]

\[ \text{1} \]
\[
\text{Br-} \quad \text{O-} \quad \text{CF}_3 \quad + \quad \text{Br-} \quad \text{OH-} \quad \text{N-} \quad \text{CF}_3
\]
Br
NNCF₃

4