Synthesis of kinase inhibitors utilizing thiophile-free *Eschenmoser* reaction of bromoindol-2-ones and thioamides

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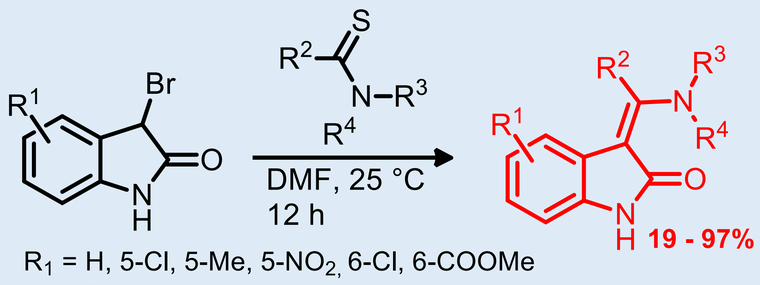
Introduction

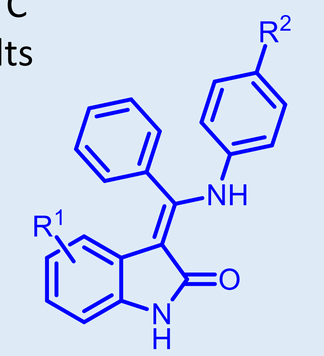
▪ **3-[Arylamino(phenyl)methylidene]oxindoles** are of significant interest in medicinal chemistry, as they acts as potent **tyrosine** or ***Aurora* A/B kinase inhibitors**. Recently, we discovered that ***Eschenmoser* reaction** of **3-bromooxindoles and thioamides** can serve as powerful tool in preparation of **substitued 3-(aminomethylidene)oxindoles**.
In this work, we demonstrate versatility of *Eschenmoser* reaction in the synthesis of several known kinase inhibitors – ***Nintedanib***, ***Hesperadin*** and their analogues.

Eschenmoser reaction - 3-bromooxindoles and thioamides

▪ An extensive study conducted with **3-bromooxindoles** and *prim./ sec./tert.* **thioamides**; no base/thiophile needed for prim. and sec. thioamides, for *tert.* thioamides – thiophile necessitate!
▪ Reaction proceeded smoothly in polar DMF at 25 °C
▪ Thiobenzanilide derivatives shown promising results



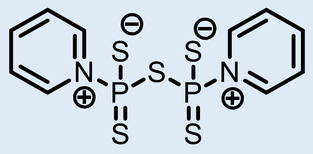
R_1 = H, 5-Cl, 5-Me, 5-NO_2, 6-Cl, 6-COOMe
R_2 = Ph, Me
R_3 = H, Me, Et, Ph, 4-BrPh, 4-ClPh, 4-CF_3Ph, 4-MeOPh, 4-MePh, Me, *n*-pentyl, chex
R_4 = H, Me, Et



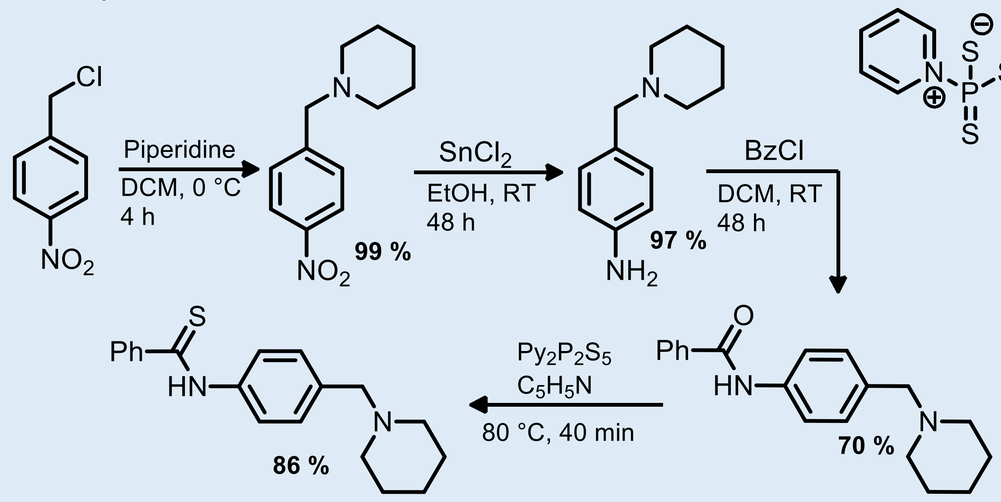
Thiobenzanilide-derived TKI pharmacophores!
Yields: 43 – 88 %

Synthesis of key thioamides

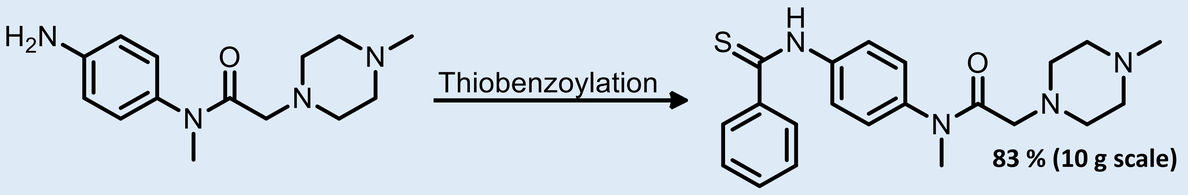
$Py_2P_2S_5$ – excellent chemoselectivity



▪ „*Hesperadin* thioamide“ – thionation



▪ „*Nintedanib* thioamide“ – thiobenzoylation (screening + scale-up)



Entry	Agent	Mol. equiv.	Solvent	Time [h]	Temp. [°C]	Conv. [%]	Yield [%][a]/ [%][b]
1	PhC(=S)SMe	1	DMF	60	100	55	50/–
2	**PhC(=S)SMe**	**2**	**DMF**	**60**	**100**	**100**	**>95/86**
3	PhC(=S)SMe	1	DMSO	60	100	50	35/–
4	**PhC(=S)SBt**	**1.5**	**DCM/DMF**	**12**	**60**	**100**	**>95/85**
5	Bn_2S_2	0.5 (0.1 I_2)	DMSO	24	100	>95	decomp.
6	(PhCS)S[c]	1	THF	0.25	– 10	15	15/–
7	$(PhCS)S_2$	1	$CHCl_3$	1	25	40	20/–

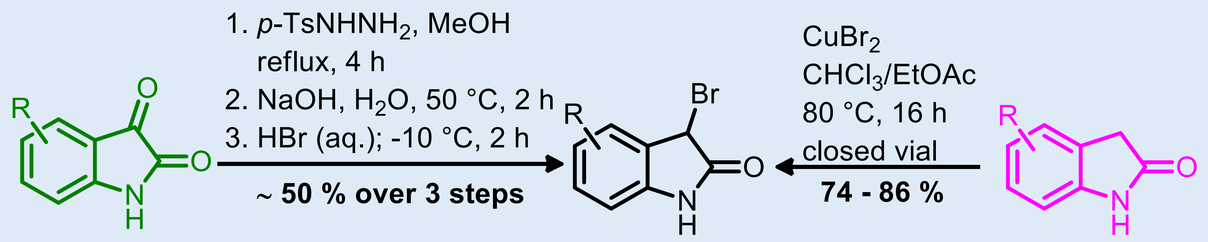
a) Assay of desired thioamide in reaction mixture b) Isolated yield (flash LC) c) Prepared „*in situ*“
Conditions: 0.1 mmol of starting aniline in 1 ml of solvent (c = 1M) in closed HeadSpace vial. Conversions determined by ^{1}H NMR after evaporation of reaction solvent.

References

[1] Roth G.J.; Binder, R.; Colbatzky, F.; Dallinger, C. et al. *J. Med. Chem.* **2015**, 58(3), 1053 – 63.
[2] Roskoski, R., Jr. Properties of FDA-approved small molecule protein kinase inhibitors: a 2020 update. *J. Pharm. Res.* **2020,** 152.
[3] Roth, G. J.; Heckel, A.; Colbatzky, F.; Handschuh, S. et al. *J. Med. Chem.* **2009**, 52, 4466 – 4480.
[4] Marek L.; Kolman L.; Váňa J.; Svoboda J.; Hanusek J. *Beilstein J. Org. Chem.* **2021**, 17, 527 – 539.
[5] Marek L.; Váňa J.; Svoboda J.; Hanusek J. *J. Org. Chem.* **2021**, 86(15), 10621 – 29.
[6] Patent WO 016530 A1 **2017**.
[7] Patent WO 068441 A2 **2012**.

Synthesis of starting 3-bromooxindoles

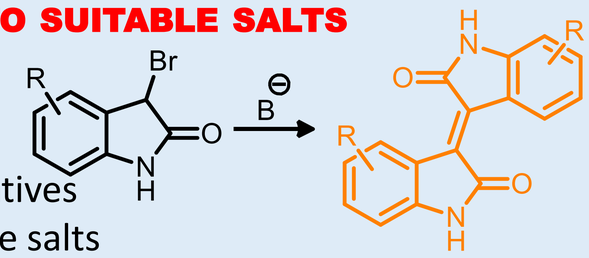
▪ Three step synthesis starting from **isatins** vs. novel method utilizing ..**oxindole** as starting material and $CuBr_2$ as mild bromination reagent
▪ Direct bromination is compatible with hydrolysable groups (e.g. COOMe)



R = H, 5-Cl, 5-Me, 5-NO_2, 6-Cl

R = H, 5-NO_2, 6-COOMe

Conversion of thioamides into suitable salts

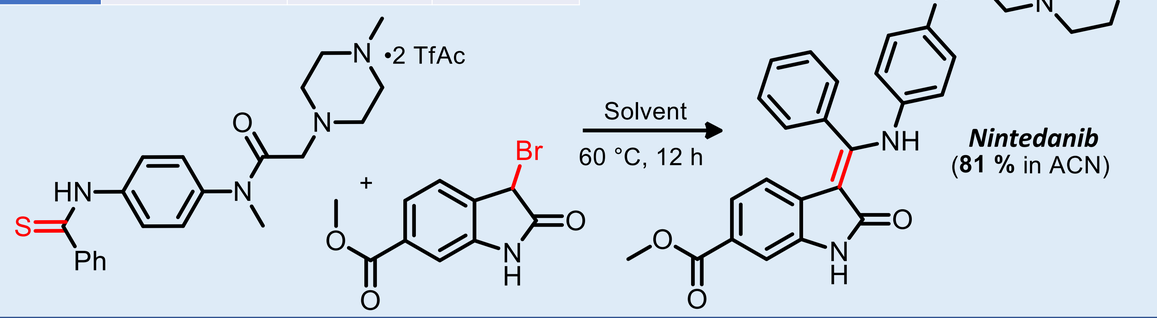


▪ Both starting thioamides contains basic centers - decomposition of 3-bromooxindoles to isoindigo derivatives
▪ Conversion of thioamides into suitable salts
▪ *Hesperadin* thioamide·HCl/*Nintedanib* thioamide·2TfAc were prepared

Synthesis of *Nintedanib* - solvent scope & scale-up

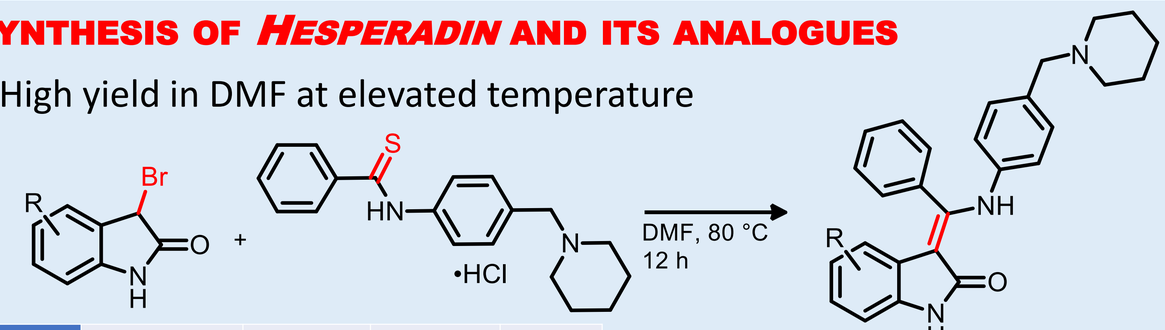
Solvent	Conversion [%]	Amide [%]	Product [%]
Acetone	91	2	89
ACN	100	3	97
DMSO	96	75	21
DMF	84	0	84
THF	73	1	72

▪ Best conversion achieved at 60 °C in ACN as reaction solvent
▪ 81 % yield in 3.3 mmol scale

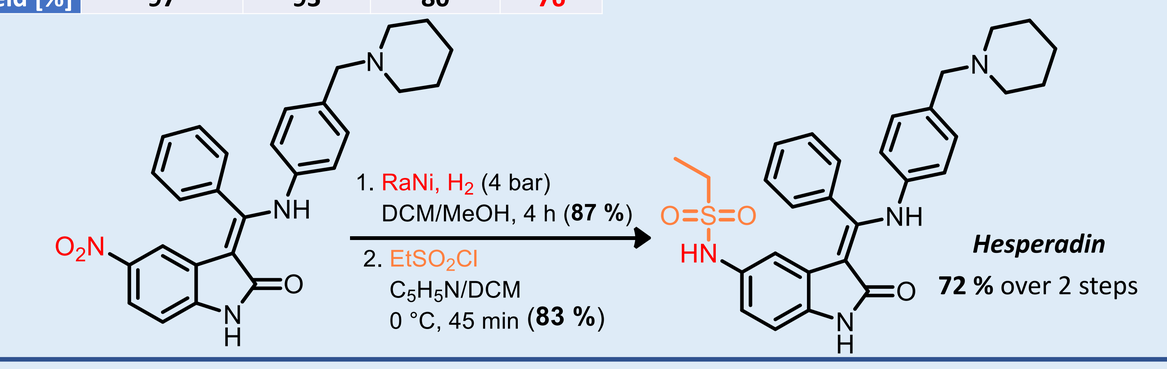


Synthesis of *Hesperadin* and its analogues

▪ High yield in DMF at elevated temperature



R	H	6-Cl	6-COOMe	5-NO_2
Yield [%]	97	93	80	76



Conclusions

- Initial study confirmed usefulness of ***Eschenmoser* reaction** for preparation of **oxindole-based TKI pharmacophores**
- Thionation of corresponding amide afforded thioamide for synthesis of *Hesperadin*
- Thiobenzoylation of commercially available aniline with *S*-methyldithiobenzoate gave „*Nintedanib* thioamide“ in high yield
- Novel synthetic method for synthesis of **3-bromooxindole by direct bromination** of oxindole developed
- ***Nintedanib*** prepared **in 81 % yield** by Eschenmoser reaction
- *Hesperadin* analogues were formed by reaction of substituted 3-bromooxindoles with „*Hesperadin* thioamide“ in DMF at 80 °C
- ***Hesperadin*** synthetized from corresponding 5-NO_2 derivative